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SYMPOSIUM ON PNEUMONIA

The following clinics are included in this Symposium:

F. D. Gunn: PATHOGENESIS OF PNEUMONIA.

Wheeler D. Sutliff: EARLY DIAGNOSIS AND SPECIFIC TREATMENT OF LOBAR PNEUMONIA.

Robert W. Keeton and Marion Hood: PULMONARY DISEASE SECONDARY TO AMEBIASIS.

Edmund F. Foley: THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PNEUMONIA.

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Ford Hick: THE USE OF OXYGEN IN PNEUMONIA.

Paul H. Holinger: SO-CALLED "UNRESOLVED PNEUMONIA": BRONCHOSCOPIC ASPECTS.



CONTRIBUTION OF DR. F. D. GUNN

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PATHOGENESIS OF PNEUMONIA

A RICH new fund of information has been acquired during the past two decades in the field of inflammatory reactions in the lung, yet considerably more work must be done before effective prophylactic control of pneumonia or its satisfactory rational therapy will be possible. Much of the knowledge that has been gained during this period has been acquired through experimental work on laboratory animals and a considerable part, even at this late date, has been obtained by painstaking study of postmortem material, correlated with careful clinical laboratory observations.

No final conclusions with regard to pathogenesis can be drawn from the results of animal experimentation unless these results coincide exactly with observations made on human material. Fortunately there are three genera of laboratory animals which appear to be suitable for pneumonia experiments in that their tissues have a susceptibility to infection with the various types of pneumococci which is closely similar to that of the human being. Of these three, the monkey, the dog and the rat, the monkey appears to have the least ability to localize pneumococcus infections of the lung and in this biologic reaction is less similar to man than the other two. The difference may be more apparent than real however, since different methods of inoculation have been used by different workers and their results have varied accordingly. As an example, the work of Blake and Cecil¹ may be cited. These workers used the *Macacus syrichtus* and *Cebus capucinus* monkeys and inoculated the lungs by injecting small doses of pneumococcus cultures between the tracheal cartilages, depending upon gravity

and chance for the distribution of the infecting dose in the lungs. As a result the pneumococci were distributed rather widely, sometimes on one side, sometimes on the other and sometimes on both sides but most of the culture remained in contact with the mucosa of the large bronchi in the region of the hilus. The percentage of successful infections was fairly high (thirty-two times with 37 normal monkeys) but the delayed development of lobar consolidation, the distribution of the lesions and their interstitial character are sufficient proof that these lesions were not all of the lobar or croupous type of pneumonia which is most commonly seen in the human adult. The lesions were frequently multiple, usually arose from the region of the hilus and fully developed lobar consolidation required from six to nine days. Shöbl and Sellards² who repeated and confirmed their work observed that the lesions produced by this method were of the nature of confluent bronchopneumonia. On the other hand, Francis and Terrell,³ using the Java monkey (*Macacus cynomolgus*) injected the infective inoculum far down into the bronchus in the majority of their experiments and observed the development of lobar pneumonia which was fully developed in three days and, clinically at least, much more nearly resembled the disease in man. Frequent observations with x-ray showed that the lesions which appeared after inoculation far out in the terminal bronchi by the method devised by Terrell, Robertson and Coggeshall¹ were located in the peripheral portions of the lung and spread toward the

of 19 *Macacus syrichtus* monkeys but found that large doses of culture were necessary to infect these animals in their natural environment. It appears then that in general the monkey is not an ideal animal for experimental investigation of the problems in pneumonia. The rabbit, the guinea-pig and the mouse are far less suitable since they show little or no tendency to localize pneumococcic infection in the lung and usually die from septicemia before any well-developed, local inflammatory response is evident. Only after partial immunization as in the experiments of Wadsworth⁷ or after forcible insufflation of massive doses of pneumococci^{8, 9, 10, 11, 12} is it possible to produce pneumonia in rabbits and even so the lesions are of the nature of a patchy pneumonia which frequently becomes confluent in one or more lobes.

While all of these experiments are valuable and indispensable for the better understanding of inflammatory responses in the lung, they are not directly applicable to the problem of pathogenesis, especially as regards the earliest stages, in the clinical-pathologic entity of lobar (croupous or parenchymatous) pneumonia in man. For this purpose, studies of the early stages of the disease in the human lung are obviously the most valuable of all but material for this is all too difficult to obtain. Of the recent studies on postmortem material, Loeschcke¹³ has published the most complete observations. Robertson and Uhley¹⁴ have studied material from carefully observed cases of pneumonia but principally from later stages of the disease. Curphey¹⁵ has attempted to study the histopathology of the various stages of development of the pneumonic lesions by the biopsy method.

By comparison of the incomplete observations on the relatively scanty human material, stage by stage, with data from the more complete and better controlled experimental pneumonia in laboratory animals, it seems to this observer that the histopathology of the earliest stages of pneumonia in dogs¹⁶ and in rats¹⁷ corresponds most closely with that of man. The monkey is not included with these principally because the published studies on the early stages of development of the disease are entirely inadequate. Blake and Cecil studied what they considered the earliest lesions in only 6 monkeys and most of these had died of pneumococcic septicemia before

consolidation had begun in the infected lung. The tendency of the monkey to develop septicemia of a high order after intrapulmonary inoculation of virulent pneumococci renders this animal a relatively poor subject for experiments of this kind, at least by the methods that have been employed up to the present time.

The concept of pathogenesis that is presented in this paper is, therefore, based upon the material obtained from post-mortem examination of closely observed clinical material and from experimental studies of the dog and the rat, with the principles of inflammatory responses, established by various experimental methods, constantly in mind.

THE INFECTING AGENT

The great majority of cases of lobar or parenchymatous pneumonia as distinguished from bronchopneumonia or patchy pneumonia, are caused by virulent strains of pneumococci and of these, 67 per cent¹⁸ or more^{19, 20} are caused by the fixed specific Types I, II and III. Rare cases are caused by *Bacillus mucosus capsulatus*, streptococci, staphylococci and *Haemophilus influenzae* but for the purposes of this discussion the pneumococcus will be considered as the causative agent of lobar pneumonia.

vidual to localize the infection through natural resistance or specific immunity. For the initiation of a progressive lesion the size of the dose is less important than virulence for, under favorable environmental conditions, as will be pointed out later, extremely small doses of virulent cocci are capable of initiating just as extensive lesions as are large doses.^{4, 16, 17, 22} However, the development and spread of the initial lesion is more prompt with the larger doses^{4, 16} and the result is more frequently fatal.

ROUTE OF INFECTION

It is now generally accepted that the route of infection is through the respiratory tract. Virulent pneumococci reach the upper respiratory tract by direct contact or droplet infection, later to be aspirated with mucous secretions into the small bronchi and alveolar ductules. Less commonly the infectious material may reach the periphery of the lung by direct inhalation of droplets. This latter method seems less likely in view of the numerous unsuccessful attempts experimentally to infect laboratory animals by exposing them to a spray of pneumococcus cultures or by spraying the bouillon cultures directly into the nose or pharynx. Yet these experiments are by no means always unsuccessful and occasionally a laboratory worker is accidentally infected in this way.²³ When, on the other hand, virulent cultures are mixed with mucus or purified, sterile mucin²² or a viscous starch paste⁴ and injected well down into the small bronchi whence the animal cannot immediately cough it out, pneumonia results in practically 100 per cent of cases. The viscous substance prevents immediate phagocytosis of the bacteria either by preventing opsonization of the pneumococci²⁴ or by mechanical hindrance of the phagocytes from contact with them since neither polymorphonuclear cells nor macrophages can enter such a medium readily.²⁵ At the same time such a menstruum tends to prevent a rapid scattering of the bacteria and it is known that a certain concentration of pneumococci and their products is essential for the initiation of the lesion, the reason for which will be explained later in detail.

Intravenous, subcutaneous or intraperitoneal injections of pneumococci never give rise to pneumonia. Animals which are

not resistant to pneumococci succumb to septicemia and highly resistant animals (dog and rat) recover without any localizing lesion in the lungs. Some writers have maintained that lobar pneumonia is hematogenous in origin but no experimental evidence and no cogent clinical or morphologic grounds have been presented to support such a theory. The chief basis for the belief is the fact that pneumococci are sometimes found in the blood of patients suffering from pneumonia before there are any clinical signs of the disease. The experimental work has furnished an adequate explanation for this observation in showing that there is frequently a transient bacteremia which appears within a few hours after inoculation of the lung and usually disappears with the inflammatory localization of the infection. The recognition of very early pneumonic lesions with the aid of x-ray examination in clinical cases and in experimental pneumonia in the larger animals^{3, 4, 16} has largely discredited the theory of hematogenous origin.

That an infection of the bronchi and peribronchial fibrous tissue with involvement of and spread through the lymphatics may precede the exudative response in the parenchyma of the lung in some cases there can be little doubt for it is supported by both clinical and experimental evidence; but in the majority of cases such a lesion assumes the form of a bronchopneumonia or central (hilar) lesion which may spread peripherally to involve one or more lobes.²⁰ These forms are more commonly encountered in children than in adults. This mechanism is observed in experimental animals when liquid cultures are allowed to trickle down the trachea and lodge on the mucosa of the

route (aspiration of infectious material through bronchi and bronchioles into parenchyma near periphery of lung) and considered by the writer to be the common mechanism in lobar pneumonia in man, that will be described, stage by stage, in the paragraphs on the development of the lesion.

PREDISPOSING FACTORS IN THE HOST

It has been pointed out in previous discussion that no special procedures such as chilling the animal, partial immunization, sensitization or other means of altering the reactivity of the tissues need to be used in the experimental production of pneumonia in suitable animals.^{1, 3, 4, 22, 27} This conforms with the usual experience in clinical work. The disease generally occurs in a previously healthy lung and in an otherwise healthy individual but sometimes the onset is preceded by a minor disturbance of the upper respiratory tract such as coryza,^{13, 20, 26} with several hours or at most a few days of minor disability. Previous infection with sensitization of the lung has been assumed by some²⁶ but sensitization to pneumococci as shown by reactivity of the skin, which has been shown to be fairly well correlated with reactivity of the lung,^{25, 29} is not found to be present in human subjects until the stage of recovery.^{30, 31} Lauche³² contended that since infants under five months of age rarely are the victims of lobar pneumonia, it must be due to their lack of sensitization to pneumococci. He further assumed that as individuals grow older they come in contact with pneumococci from time to time and become sensitized by mild unrecognized infections, thus preparing the lung for a time when it may become infected with a potent dose, resulting in a major inflammatory response. He regards the rapid onset of pneumonia as an allergic response to infection occurring in a sensitized individual. If this were true, a large proportion of the population should be found to be sensitive to one or more types of pneumococci whereas specific sensitization in patients not recently recovered from pneumonia has been demonstrated with considerable frequency in only a small group of patients suffering from various diseases³¹ and in these a recent pneumococcic infection had not been excluded. Furthermore, if hyperergy or increased reactivity of the lung were the most important factor in enhancing the rapid

development of the exudative lesion which follows infection, an animal which has recovered from a previous infection with pneumococci would be expected to react to a second infection with the homologous type with the formation of a more severe and more extensive exudative reaction in the lung. The contrary has been found to be the case.³³

It has been known for a long time that certain external factors predispose the individual to acute pneumonia. Such factors as exposure to cold with chilling of the body, inhalation of poisonous gases including anesthetics, alcoholic intoxication and traumatic injury of the lung as produced by a severe blow on the chest are observed to be followed by pneumonia in a noteworthy but highly variable percentage of cases. A possible common denominator of these apparently unrelated influences is edema of the parenchyma of the lung. Of all factors in the host that determine the suitability of the tissue as a site for a progressive pneumococcic infection, excepting only that of local and general specific immunity, the presence of edema fluid is predominant. Edema fluid forms a favorable culture medium, practically free from antibodies and phagocytes, in which the bacteria proliferate at a rapid rate, liberate toxic products which, carried into adjacent tissue by the fluid, stimulate further exudation at the spreading margin of the now established lesion. The serum of the exudate, even though possessing high opsonizing power, has no inhibiting effect upon the rate of propagation of the pneumococci in the period previous to the active mobilization of the phagocytic cells, since the only antibacterial effect of immune serum is through its agglomerating power and the preparation of the cocci for phagocytosis and intracellular digestion. Phagocytosis is further delayed in the nonimmune animal by the inhibiting effect upon the phagocytes of the specific carbohydrate which is liberated by the pneumococci and is carried by diffusion through the fluid medium.

Another possible mechanism by which various external factors may assist in establishing a progressive infection of the lung has been described by Nungester and Jourdonais.²² They have furnished experimental support for the idea that mucinous secretions, when aspirated with virulent pneumococci even in extremely small doses, will enhance the pathogenicity of the

bacteria by protecting them from phagocytosis during the critical period while the lesion is becoming established in the lung. This enhancement of effective "virulence" by mucus, they believe, may be the determining factor in inducing pneumonia in conditions such as the common cold, ether anesthesia, inhalation of irritating gases and chilling of the skin, in which there is an increased quantity of mucus in the respiratory tract.

MECHANISM OF DEVELOPMENT OF THE LESION

For reasons already cited the details of the histopathology of the earliest stages of the lesions must be obtained largely from the study of lesions in experimental animals. The intensity of the inflammatory reaction during the first five or six hours is directly dependent upon the size and distribution of the infecting dose and especially upon the concentration of bacteria in any given area. When the inoculum is introduced in such a way that the irritating agent is dilute (only a few bacteria present in a high power field of a microscopic section taken from the injected site), the alteration of the tissue at the end of an hour is very slight. At this time there is slight dilatation of the capillaries, the beginning of infiltration of polymorphonuclear leukocytes, slight exudation of edema fluid in the alveolar spaces and evidence of irritation of the septal cells (alveolar epithelium)* in the form of uneven swelling and protrusion into the alveolar lumens. In the more heavily infected foci the infiltration, largely intra-alveolar in character and most abundant in the immediate vicinity of the bronchial stem and its branches,¹⁶ may contain numerous erythrocytes and abundant edema fluid. The small bronchi themselves show slight damage to the epithelial lining and occasionally there is a scanty leukocytic infiltration of the peribronchial fibrous tissue. The beginning of perivascular edema may appear around the larger blood vessels as early as one hour but it is more prominent in and more characteristic of later stages.

* In this paper the terms "septal cell" and "alveolar epithelium" are used synonymously. It is assumed by the writer on the basis of his own observations and those of many other experimenters that most of the macrophages (large mononuclear phagocytes) that are found in the alveoli are derived by proliferation and separation from the alveolar walls of the septal cells or alveolar histiocytes.

During the first six or eight hours the rapid accumulation of exudate in the area of inoculation results in an overflowing of fluid into the surrounding alveoli and bronchioles, transporting bacteria with it. Within the limits of the primary site (the site of inoculation) the capillaries become increasingly engorged with blood; the air spaces are filled with edema fluid in which leukocytes become more and more abundant; the septal cells swell, many become detached from the walls and are found mixed with the blood cells in the alveolar exudate. In most instances the mononuclear phagocytes* form a very small percentage of the cells but during the early stages they appear to be more active in engulfing pneumococci than are the polymorphonuclears which are much more numerous. At the periphery of the primary site the widening zone of edema fuses with other small foci of similar nature and in from six to twelve hours the process, which up to this time has retained the form of a peribronchial or peribronchiolar pneumonia, now becomes diffuse and for the first time assumes the gross and microscopic appearance that is recognized as the "lobar" form. Fibrin appears in the exudate in from one to three hours, first as granules or single strands, later as a network of fine intersecting threads in the alveoli. The relative quantity of fibrin depends roughly upon the virulence of the pneumococci and their concentration in the tissues, *i. e.*, upon the degree of damage to capillary endothelium, affecting its permeability. The factor of increased permeability is further illustrated by the presence of large numbers of erythrocytes in areas which contain exceptionally large amounts of fibrin. As the cocci continue to increase in number in the tissue up to twelve or eighteen hours, so also the fibrin continues to appear in greater abundance during this period and later. Active phagocytosis then supervenes and during the second twelve hours, commencing perhaps even earlier, stainable bacteria in the older portions of the lesion show a rapid decrease in number, only a few cocci appearing within leukocytes and none extracellularly in the compact cellular exudate. In the edema zone at the periphery the reverse is true. Here in the cell-poor areas, pneumococci continue to proliferate in edema fluid and, according to the concept of Loeschcke, they are drawn with each respiratory effort from areas of higher pressure (edematous areas) to those of

* See footnote, page 11.

lower pressure, the negative pressure being increased in normal aerated tissue with each inspiration. The pneumococcus-laden fluid passes readily through the smaller respiratory passages from lobule to lobule and through the alveolar ductules and inter-alveolar pores directly from one alveolus to another. Bacteria reach the bronchial lymph nodes within a few hours after infection of the lung and the same type of inflammatory reaction is seen as in the latter, namely, an increase of fluid, proliferation of macrophages and infiltration of leukocytes. As progressive extension of the primary pulmonary lesion reaches the pleural surfaces the effects of irritation appear as deposits of fibrin and polymorphonuclear cells on the serous surfaces.

Peribronchial and perivascular edema is evident even in the earliest phase of the process and becomes progressively more prominent with the progress of the lesion in the parenchyma. Soon after leukocytes appear in the alveoli they may be seen also in the widened septa, in the interstices of the peribronchial and perivascular connective tissue and in the lymphatic channels. When erythrocytes form a considerable element of the alveolar exudate, they begin to appear in the lymph channels and in the peripheral sinuses of the bronchial lymph nodes.¹³ Fibrin, on the other hand, is precipitated in the stroma in perceptible quantities only after several hours and in the milder cases may be present in traces only.

Following the complete filling of the alveolar spaces with leukocytes and fibrin, and erythrocytes in variable but usually comparatively small quantities, the peak of development of the lesion may be considered to have been reached. It is a transient phase and unless the process has spread over the entire lobe with extreme rapidity, it is represented in the lung as seen grossly by an uneven, frequently narrow, gray or grayish red zone between the zone of edema and the older area of gray hepatization. This is the only "red" stage that can be said to intervene between the stage of edema and the stage of true hepatization in the ordinary case of lobar pneumonia.

The next stage which is of considerably longer duration may be designated on the basis of its histologic picture as the fibrin stage and corresponds in the gross to the stage of hepatization. By the time this phase has been fully developed, the precipitation of fibrin has reached a maximum and leukocytes have dis-

appeared from the fibrin meshwork over fairly large areas, presumably through active migration since remnants of disintegration of cells are the exception rather than the rule. Capillary engorgement has given way to ischemia as the result of distention of the alveoli with exudate and most of the fluid has drained away, leaving a comparatively dry tissue, tightly filled with fibrin. In such tissue and exudate, pneumococci usually are very few. This picture appears in lobar pneumonia in two to five days after the first clinical symptoms of the disease¹³ (in experimental pneumonia in rats, in twenty-four to forty-eight hours after inoculation¹⁷). The erythrocytic component of the exudate at first remains in place and, in patches where erythrocytes are abundant, imparts to the gross picture a light red color. This appearance is sometimes designated as "red-gray hepatization" but the red portion is usually so insignificant that the term seems hardly justified.

The stage that follows gray hepatization, that of fibrin shrinkage, is the only stage in which erythrocytes are sufficiently numerous to impart a decidedly red color to large areas or even to an entire lobe¹³ while fibrin is at the same time sufficiently abundant to give a firm consistency (hepatization). In experimental animals shrinkage of fibrin occurs in two to five days; in man, usually a longer time is required—four to seven days in the clinically well documented cases of Loeschcke. With this shrinkage, the release of pressure allows the alveolar capillaries again to become distended with blood; there is an escape of erythrocytes into the alveoli for the second time but this time they are not intimately mixed with the fibrin and lie between the alveolar wall and the plug of compact fibrin in the center.¹³ Thus, if the secondary hemorrhage is abundant, a "red" stage occurs after the stage of gray hepatization which may with some justification be spoken of as "red hepatization," whereas such a picture when observed at necropsy is almost always misinterpreted as an early stage of pneumonia, following immediately the stage of engorgement and edema. While this interpretation (that of Loeschcke) does not as yet have full confirmation in experimental work, it furnishes a reasonable explanation for the nearly universal difficulty in demonstrating a red fibrinous stage (true red hepatization as distinguished from engorgement with nonfibrinous consolidation)

between the stage of edema and the stage of gray hepatization and the further embarrassment in attempts to explain why large red "hepatized" areas may sometimes be found in a lobe which otherwise is pale, solid and yellowish gray and which from the clinical and x-ray data would be expected to be in a late stage of hepatization. It seems probable that in many cases the secondary bleeding after shrinkage of fibrin is inconspicuous and thus the stage of true red hepatization is skipped entirely.

The final stage of pneumonia is reached in a most insidious manner and is difficult to confine within definite limits of time. Resolution or the process of removal of the fibrinous exudate is seen frequently in the oldest portion of the lesion as early as the third day (any time after the first twenty-four hours in dogs and rats). It spreads from many foci, in the case of successful tissue response, to the entire field of consolidation, requiring two to three weeks but occasionally as long as four weeks for the complete solution of fibrin. As to the relative importance of the macrophages and the leukocytes with their fibrinolytic enzymes only this can be said, that the complete disappearance of fibrin can take place in the absence of leukocytes but that it is never observed to take place in the absence of macrophages.^{13, 14, 17}

Previous mention has been made of the appearance of the macrophages in relatively small numbers even in the earliest stages of the lesion. At first they appear to be engaged only in the occasional phagocytosis of bacteria but after the migration of leukocytes into the alveolar spaces in large numbers the macrophages are frequently seen to contain leukocytes and fragments of erythrocytes. From this time until resolution begins they seem not to increase in number but rather to diminish if anything, for in the large fibrin-rich areas the alveoli contain very few mononuclear cells. However, with the gradual diminution of fibrin following the stage of shrinkage, macrophages become more and more numerous and the more numerous the mononuclears the less the fibrin in any particular area. In the words of Loeschcke, "Das Alveolarepithel wächst auf dem Fibrin wie ein Explantat auf einem künstlichen Nährboden und zehrt allmählich das Fibrin vollständig auf" (the alveolar epithelium grows upon the fibrin like an explant upon artificial culture medium and gradually consumes the fibrin

completely). As fibrin disappears from the alveoli, the size of the space diminishes and the capillaries may appear to contain even more blood than in the initial stage of engorgement. Since much of the liquefied exudate is removed by absorption the tissue becomes atelectatic and remains so until the obstructing cylinders of exudate in the bronchi are coughed up. The loosening of these fibrinocellular masses, which sometimes obstruct the bronchi even of the second and third orders, is brought about in part by the action of macrophages which migrate into the bronchial lumens where they are found at the periphery of the fibrinous masses.¹⁷

MODE OF EXTENSION

From the preceding discussion of the development of the lesion it can be readily surmised that there are two common routes of extension of pneumonia from one lobe to another. In the case of involvement of contiguous lobes, the process may extend directly to the parenchyma of the uninvolved lobe in places where the interlobar septum is deficient, at the base of the fissure, and the process will then spread toward the periphery of the lobe. If, on the other hand, reaspiration of pneumococci-laden fluid from the bronchus of the involved lobe takes place, the metastatic focus will usually be located in the periphery or midportion of the lobe. Since the direction of flow of fluid exudate is largely determined by gravity,^{13, 34} the posterior portions of the lungs are much more frequently involved in the bedridden patient. The evolution of the metastatic foci is simply a repetition of that of the initial focus. Theoretically, if a sufficiently large volume of infectious fluid should be aspirated at one time and spread widely throughout a lobe, an exudative process would be initiated in which each stage would evolve simultaneously throughout the lobe; in other words each of the successive stages, the stage of edema, the stage of leukocytic infiltration and the stage of hepatization would present a more or less homogeneous gross and microscopic picture throughout such an area at any given time. Just such an occurrence has been described in human cases by Loeschcke.¹³

Obviously in a limited space it is not possible to discuss the evidence on both sides of such controversial subjects as the

rôle of previous sensitization to the pneumococcus in the development of pneumonia, the concept of the reversal of flow of lymph in the lung and its rôle in the pathogenesis²⁶ and the influence of local and general immunity upon subsequent infections. With regard to the last, Coggeshall and Robertson²² have shown in a convincing manner that in experimental animals the chief effect of active immunity is to speed up the evolution of the lesion, lessen its extent and bring about a much more rapid resolution of the exudate through the more rapid mobilization of macrophages in the infected lung.

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EARLY DIAGNOSIS AND SPECIFIC TREATMENT OF LOBAR PNEUMONIA

As type specific antipneumococcic sera come into more general use in the treatment of early cases of lobar pneumonia, the details of clinical reports of the disease take on new aspects. Two cases of lobar pneumonia are reported below which illustrate what the physician, who is alert to make a definite diagnosis at the earliest moment, will see. Both patients are young men of the age group in which the disease takes on its most classical form. Such differences as they show from the common descriptions of the disease are probably entirely due to the fact that they were seen within the first three days of illness. The case reports indicate that laboratory facilities offer a considerable aid in early diagnosis. The technic and results of serum administration are also described.

Case I.—Patient A. H., a student in the University of Chicago, twenty-three years of age, was quite well until the morning of January 3, 1937. He awoke with a sharp pain in his left chest and a feeling of general malaise. He visited the Student Health Service where his temperature was found to be subnormal. He was sent home but returned after two hours and was admitted to the hospital.

It was learned that the evening before the onset of his disease he had ridden in the rumble seat of a car for a considerable distance without a hat. His past history showed that he had had pneumonia at four years, was subject to asthma until the age of twelve, and hay fever at the present. He had had an infection of the cervical lymph glands with operative removal at the age of thirteen years.

Physical examination showed very slight dulness at the base of the left lung with diminished breath and whispered voice sounds. His white blood count was 19,000 and x-ray examination of the lungs showed a generalized prominence of lung markings, but no localized shadows. Cultures of his blood were made on admission and these proved the most valuable diagnostic aids. His blood culture was positive for Type I pneumococcus. His sputum obtained

twenty-four hours after admission also showed Type I pneumococci by Neufeld examination.

During the first twenty-four hours in the hospital he continued to have pleural pain. A chill occurred twelve hours after admission. His temperature remained between 101° and 103° F.; the pulse rate was 36 and respirations were between 22 and 28 per minute. Specific serum therapy was begun at 2 P. M. on January 4th, twenty-three hours after admission; 3000 units of Type I concentrated antipneumococcic serum were administered intravenously, after it had been ascertained that he had no specific horse serum sensitivity by means of intradermal and conjunctival test and history. Further serum was administered as follows:

January 4: 3 P. M., 17,000 units
5 P. M., 20,000 units
• January 5: 5 A. M., 20,000 units
9 A. M., 20,000 units
12 noon, 20,000 units

Urticaria developed after the third and last doses of serum. His temperature rose to 106° F. at 4.30 P. M. on January 4th and thereafter fell sharply to normal on January 5th. His chest pain was relieved completely during serum administration. x-Ray examination on January 4th showed a small shadow in the left lower lung field and on January 7th showed some clearing of the lesion. He was discharged from the hospital on January 13, 1937, to rest at home.

Case II.—Patient G. P., aged twenty-nine years, had arrived in this country from Germany two weeks before. He entered the Surgical Service of Billings Hospital on February 1, 1937, and had a draining sinus of the thoracic wall removed. This draining sinus had been the result of a rib resection for empyema one year before. He was discharged from the Surgical Service on February 10, 1937. On the day of discharge he began to feel badly with headache, fever and slight cough. These symptoms continued for two days at home. His temperature was found to be 103° F. and he returned to the hospital on February 12, 1937.

Physical examination on admission to the hospital revealed him to be acutely ill. The operative wound in the left lower chest appeared to be almost completely healed with slight tenderness and edema at the upper end. His temperature continued 103° F., pulse rate 130, respirations 24 to 32 per minute. He brought up a small amount of rusty sputum on February 13th and began to complain of pains in the upper right chest anteriorly. Although the initial examination on February 12th showed no changes in physical signs, it was now found that there were some fine râles and slight accentuation of the breath sounds beneath the right clavicle.

His white blood count was 53,900, polymorphonuclear cells 88 per cent, lymphocytes 12 per cent. On Neufeld examination the sputum showed pneumococcus Type VII in pure culture. Blood culture was negative. x-Ray examination of the lungs showed clouding of the midportion of the right lung field.

The diagnosis of infarction of the lung was considered but the bacteriologic examination and a marked febrile and leukocytic reaction indicated that infection was the chief factor.

Specific serum therapy was begun at 6 P. M. on February 13th, after ascertaining that the patient had no history of reactions to horse dander or horse serum, that his conjunctival test to horse serum was negative, that his skin test to horse serum was moderately positive (erythema 2 cm. in diameter, no wheal). Polyvalent Type VII and V concentrated antipneumococcic serum, containing 10,000 units of Type VII antibodies, was administered intravenously, taking fifteen minutes for the injection. Serum therapy was continued by the administration of 20,000 units of Type VII antiserum at 8 P. M., 30,000 units at 10 P. M. and 40,000 units at 12 midnight. His temperature fell to normal by 8 A. M., February 14th, rose to 100.8° F. at 4 P. M. the same day, and was normal thereafter. He felt well the day after serum administration and continued to an uneventful convalescence with the exception of arthralgia from February 22nd to 25th, associated with fever to 100.2° F. on February 23rd. He was discharged from the hospital on March 2nd in good condition.

Diagnosis.—The recognition of pneumococcic lobar pneumonia within one, two or three days after the onset depends most often upon the evaluation of symptoms: fever, chill, pleural pain, pneumococcic sputum. In some cases physical signs of consolidation may be of definite value. x-Ray examination of the chest may be performed in hospitalized patients and this may aid in interpreting physical signs. Less attention has been paid to the diagnostic significance of quick and accurate identification of the infecting micro-organism. In both of the patients described above the relative diagnostic values of these characteristics of lobar pneumonia are brought out.

Symptoms.—In the first case fever, prostration and pain in the chest were the outstanding manifestations of the infection. A chill occurred within twelve hours after admission. In the second case fever and prostration were present for two days followed by the development of pain in the chest and bloody sputum. These symptoms were interpreted in both instances as indicating the probability of pneumococcic lung infection.

Physical Signs.—In both cases physical signs were insufficient to contribute definite confirmation of the diagnosis. In the first case no definite information was obtained from physical signs until the fourth day after onset, when a small patch of râles and increased intensity of breath sounds were found

at the base of the left lung posteriorly following examination of the x-ray films. In the second case physical signs of consolidation were present but these did not suffice to distinguish between the alternative diagnoses that were presented, namely, infarction of the lung and pneumonia.

Roentgen Ray Examination.—Increased density of lung markings was an early finding in the first case. A small area of increased density appeared in the left lower lung field on the fourth day and later disappeared. This did not aid in early diagnosis but confirmed our interpretation that the infection was localized in the lungs. In the second case the roentgen ray showed the extent, location and density of a consolidation, the presence of which was already known.

Pneumococcus Cultures and Typing.—In the first case the blood culture made on admission was found positive eighteen hours later for Type I pneumococci. It thus became a most significant finding in the recognition of Type I pneumococcic pneumonia in connection with the other features of the case. The patient did not have any sputum until after the result of the blood culture was known. When sputum was examined Type I pneumococcus was again found. In the second case sputum was available shortly after admission to the hospital. Examination by the Neufeld technic showed the presence of Type VII pneumococci in large numbers. The finding of virulent pneumococci in the sputum pointed toward the presence of lobar pneumonia and when taken into consideration with the rest of the findings was the principal evidence for the diagnosis of lobar pneumonia instead of infarction of the lung.

These 2 cases are typical of many that are seen wherever great emphasis is placed upon the early diagnosis of pneumonia. The experience of Fraeser, Wu and Robertson confirms the impression gained from this case that the greatest reliance should be placed upon the history of the disease. In a study of 24 patients in whom the disease was recognized thirty hours or less after the onset, they found that no respiratory symptoms were present in only 1 case and in this case chill, headache, prostration and leukocytosis appeared suddenly and thus aided to some extent in pointing to the possibility of the presence of lobar pneumonia. Roentgenographic signs of consolidation were absent in 2 cases of their series. Physical

signs of consolidation were absent in 4 cases. In the majority of cases history, physical signs and x-ray all were helpful in making the diagnosis and thus lobar pneumonia is usually quite easy to recognize in the first thirty hours. It is obvious, however, that where difficulty is encountered it is usually due to difficulties in demonstration of pulmonary involvement and that the history of onset is the most reliable feature for use in early diagnosis.

In the past references to pneumococcus typing with relation to its usefulness in diagnosis have emphasized the obvious fact that it alone does not indicate the presence of lobar pneumonia. But many instances arise when the recognition of type specific pneumococci is of value in diagnosis. If it is desired to diagnose pneumonia within the first three days after onset, the finding of a pneumococcus in sputum or blood of a type which is known to occur frequently in pneumonia and rarely in the mouths of healthy persons, such as Type I, Type II, Type V, Type VII, Type VIII, is of considerable significance.

Serum Therapy.—The general rules which we have followed in the administration of concentrated type specific anti-pneumococcic serum are as follows:

Precautions are taken to prevent reactions due to horse serum sensitivity. The patient is questioned in regard to his allergic background, asthma, hay fever, eczema, urticaria in himself or in his family, and particularly with reference to asthma on contact with horses, and previous experiences with horse serum injections. A conjunctival test is performed by dropping 1 or 2 drops of 1:10 dilution of horse serum into the conjunctival sac. Injection of conjunctival vessels appearing within twenty to thirty minutes indicates serum sensitivity. An intradermal test with 0.1 cc. of 1:100 horse serum dilution is also performed and observed for twenty to thirty minutes for the possible development of a wheal and erythema reaction. The history and tests are not considered equally significant in indicating the possibility of serum sensitivity. A positive eye test is the most significant finding and horse asthma or anaphylactic response to previous serum injections also indicates the possibility of serious results from intravenous horse serum injection. If positive conjunctival tests or a definite history of sensitization are present, serum may be given only with the

greatest caution. If other indications of allergic tendencies are present, no precautions other than those routinely employed are necessary.

Precautions against reactions that do not depend upon the sensitization of the patient but are inherent in all intravenous medication are also taken. The serum which usually comes directly from a refrigerator is warmed to 20° to 30° C. The syringe is sterilized by dry heat or, if boiled, thoroughly freed of water. The first dose is administered quite slowly, about five minutes being required for the first cubic centimeter and ten minutes more for the remaining 4 to 9 cc. The patient is observed closely during injection and the injection is stopped if his face becomes flushed or breathing labored or pulse rate unduly increased, or if he complains of pain or discomfort, especially in the back or chest. A hypodermic syringe with adrenalin is kept available for immediate use whenever serum is being given.

Dosage.—Type I pneumococcic pneumonia patients are usually given 50,000 units of Type I antibodies. The first dose contains 10,000 units, the second 20,000 and the third 20,000. These are given at two-hour intervals. Type II pneumococcic pneumonia patients are usually given 100,000 units of Type II antibody. The doses are likewise given at two-hour intervals as follows: 10,000 units, 20,000 units, 30,000 units, 40,000 units. It is probably wise to give patients at least 100,000 units when Type V, Type VII, Type VIII or Type XIV infections are being treated. Under certain circumstances which indicate the presence of a more severe infection, it is our practice to double the dosage already mentioned; namely, when bacteremia is present, when patients are more than sixty years of age, in pregnancy, or when more than one quarter of the lung tissue is consolidated.

The first patient illustrates several of the points with regard to serum administration. He had a history of asthma and hay fever, but he knew of no sensitivity to horse dander and his eye test and skin test to horse serum were negative. No precautions other than those already mentioned were taken in regard to serum administration and with the exception of two brief urticarial reactions after the third and the last doses of serum respectively no difficulty was encountered. Persons with

such an allergic diathesis are probably more apt to have serum reactions than others but in the absence of severe specific horse serum sensitivity, suitable care in serum administration will prevent serious results.

Another unusual feature in Case I was the presence of a bacteremia so early in the course of the disease. Because of its serious prognostic significance, 100,000 units of Type I antipneumococcic serum were administered.

The second patient illustrates the treatment of a patient with Type VII pneumonia. He had no history of allergic reactions but his skin test to horse serum was moderately positive. No precautions other than those that are always taken were employed and no immediate serum reactions were encountered. He was given 100,000 units of Type VII antipneumococcic serum with an immediately favorable result and had an uneventful convalescence with the exception of mild serum sickness appearing nine days after serum treatment. The symptomatic response in this case of Type VII pneumonia was similar to that observed by others in rather large groups of patients. It is becoming apparent that good results may be obtained in Type V, Type VII, Type VIII and Type XIV pneumococcus pneumonias by means of specific serum therapy administered early in the course of the disease. The following table gives the mortality rates reported by a number of authors in the recent literature:

EARLY TREATED CASES WITHOUT CONTROLS

Type	Per cent died	Number of cases
V	9.6	93
VII	6.3	47
VIII	8.8	47
XIV	7.1	28 (children)

Most observers feel at the present time that type specific serum administered early is the only curative measure for pneumococcus pneumonia and that developments that are now under way will make this type of therapy applicable to nearly all cases that are seen in practice and will allow of its distribution to all patients, regardless of cost, who are in need of such treatment.

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PULMONARY DISEASE SECONDARY TO AMEBIASIS

INVOLVEMENT of the lung as the result of amebic infection of the liver is more common than is usually suspected. The difficulty in making the diagnosis arises largely out of failure to consider this correlation. Several cases recently seen have been so instructive as to warrant a critical presentation. Success in the treatment of the condition makes it imperative to arrive at a correct diagnosis. If proper treatment is given reasonably early the patient lives; if not, he dies.

A more or less continuous study of amebiasis has been carried on since the discovery of the causative organism in 1875 by Lösch. It was early recognized that the amebae were not always confined to the intestine but that they migrated through the blood stream producing abscesses, whose rupture might further spread the disease. Futcher¹ reported 118 amebic cases in the medical wards of Johns Hopkins Hospital during the first fourteen years of their operation (1889-1903). This comprised 0.74 per cent of all the medical cases. Of these, 27 or 22.6 per cent developed liver abscesses, 9 of which ruptured through to the chest cavity. Two of these latter cases were discharged improved.

Craig² cited the results of 8 observers. This group reported 604 cases of liver abscess, 190 of which ruptured. Of these, 117 ruptured into the chest cavity, 70 into the pleura and 47 into the lung. One of these cases of amebic infection of the lung which came under Craig's own observation³ was a primary infection. In his book² "Amebiasis and Amebic Dysentery" Craig states that this is the only such case he has seen. Rouil-

lard⁴ observed that Petzetakis was the first person to call attention to amebic bronchitis without abscess. He concluded that amebic dysentery was not a local intestinal disease but a general infection caused by the passage of amebae into different organs through the circulation.

The alkaloids in ipecacuanha were used as early as 1829 by Bardsly (quoted by Craig²). Owing to their ineffectiveness and toxicity their use was largely discontinued. Not until 1912 when Vedder demonstrated that the amebicidal effect was in the single alkaloid emetine was its use reestablished in the form of emetine hydrochloride. Biggam and Ghalioungui⁵ stated that since the introduction of emetine and other more recent drugs in the treatment of amebic dysentery, amebic liver abscesses had become relatively uncommon in Egypt but that cases still occurred from time to time. During eighteen months they had had 25 cases of amebic liver involvement, 3 of which showed lung complication.

The following cases from the Out-patient Dispensary and the Research Hospital of the University of Illinois College of Medicine illustrate some of the problems presented by pulmonary disease secondary to amebiasis.

Case I.—J. H., presenting history of long-continued fever and evidence of diaphragmatic pleurisy.

History.—This patient entered the hospital July 15, 1937, with the complaint of fever, chills, and pain in the right side and shoulder. The symptoms of chills and fever had started three years previously, at which time the diagnosis of malaria was made and the patient was given quinine. This therapy did not relieve the condition. In January 6, 1937, he was given atabrin, the doctor still believing the source of the trouble to be malaria. The patient thought this drug poisoned him as he was turning yellow. At this time he went to Hot Springs for baths which helped the pain but the other symptoms continued. On March 29, 1937, because of the pain in the right side his gall-bladder and appendix were removed. These were apparently normal. However, his condition materially improved and remained so until July 4, 1937, at which time all symptoms returned. The pain in the right shoulder became sharp and cutting. Coupled with these complaints was a subnormal weight and an inability to gain due to his poor appetite.

Examination revealed that the liver was tender and enlarged to about 2 fingerbreadths below the costal margin. There were no palpable masses and no abdominal fluid. At this time the impression of the case was toxic hepatitis or infectious hepatitis on the basis of malaria or amebiasis. As no malarial parasites could be found and toxic monocytes were present it was considered a

chronic toxic process with localized pus present. He was sent to the otolaryngological department but their findings showed no evidence to account for the septic type of temperature. The fluoroscopic and chest film showed elevation of right diaphragm suggestive of pressure from below. There was no evidence of intrathoracic pathology. On July 20, 1937, a stool specimen was sent to the laboratory in which were found *Endamoeba histolytica* trophozoites. On the following day a pleural friction rub in the right axillary region at the level of the seventh and eighth ribs was heard. This was accompanied by some impairment of resonance. This together with the other findings established the diagnosis of amebiasis complicated by amebic liver abscess and early pleural involvement. Emetine hydrochloride therapy was instituted the same day with the following effect on the peaks of temperature.

7/15/37.....102° F.	7/20/37 . . . 103° F.	7/24/37	99° F.
7/16/37			
7/15/37.....104° F.	Emetine started	7/25/37....	98.6° F.
7/17/37.....103° F.	7/21/37 ... 102° F.	7/26/37....	98.5° F.
7/18/37.....102.5° F.	7/22/37 102° F.	7/27/37....	97.5° F.
7/19/37.... 102.5° F.	7/23/37 100.5° F.	7/28/37 . .	98° F.

The patient's progress was satisfactory. His temperature reached normal, and he remained pain-free. Eight grains of emetine hydrochloride have been given followed by a course of chiniofon.

Comment.—This patient had an obscure fever of three years' duration, the source of the infection not being located. He was treated for malaria and had a gallbladder operation without influence on its course. The elevation of the diaphragm on the right side, coupled with a tender liver measuring somewhat larger than normal made the diagnosis of liver abscess strongly presumptive. The examination of the stool revealing amebae verified the diagnosis.

The extension of the process to the pleural cavity was just beginning. Pain was present over the shoulder and lower chest. There was a friction rub. x-Ray showed some clouding at the costophrenic angle. The patient obviously had a diaphragmatic pleurisy, which was spreading to the thoracic wall.

Case II.—F. K., presenting history of diarrhea with evidence of pleurisy with effusion.

History.—This case, a man forty-six years old, was transferred to the hospital from the out-patient department on October 11, 1934. He complained of bloody stools which had persisted intermittently for one year. Increasing weakness had been felt over this period. Dizziness and a loss in weight of 22 pounds had been noted during the preceding three months. For three weeks before

admission he had pain in the right side at the level of the eleventh rib. There was no cough or expectoration but the chest was emphysematous. The proctoscopy report from the dispensary described an obstruction due either to carcinoma of the colon or possibly amebic ulceration. The stool examination at the time showed ameba-like bodies but the type was not determined. The white blood count showed 22,500 with a preponderance of neutrophils. Otherwise it was not significant.

By October 15, 1934, the pain in the right side had become much more severe. This pain radiated to the right shoulder and was aggravated by breathing and body motion. A proctoscopy performed at this time showed a granuloma at about 20 cm. Microscopic examination of the feces demonstrated many cysts and a few trophozoites of *Endamoeba histolytica*. The diagnosis of liver abscess complicating chronic amebic dysentery was then made. The patient

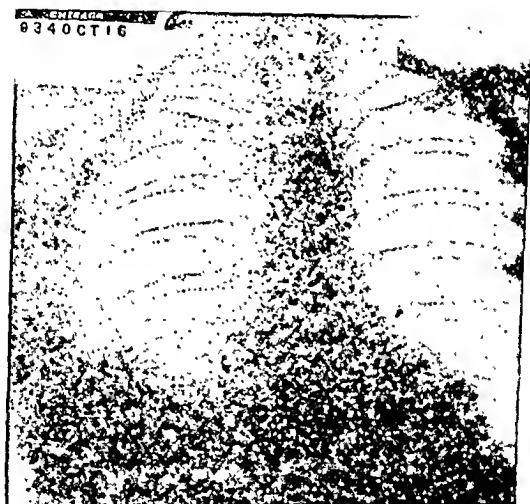


Fig. 1.—Pleurisy with beginning fluid formation.

was given a course of chiniofon. On October 16, Fig. 1 was taken, which showed a diffuse density above the right diaphragm indicating fluid in the pleural cavity. On October 23, the patient complained of severe pleural pain in the right side. Figure 2, taken October 29, showed evidence of fluid in the right pleural cavity extending to the level of the first interspace.

A thoracentesis done the following day removed 5 cc. of straw-colored fluid, containing no pus and no blood. On November 4, 1934, a course of emetine hydrochloride was instituted. The patient was discharged on November 12, 1934. At this time the proctoscopy showed considerable improvement in the condition of the colon, there were no râles or friction rubs and the patient was completely free from pain. The fluid had disappeared from the chest. The discharge diagnosis was amebic granuloma of the colon, subphrenic abscess and pleurisy with effusion.

Comment.—This patient entered with a diarrhea and a mass in the sigmoid, the character of which was not entirely clear. It appeared to be a granuloma. There was pain at the level of the eleventh right rib anteriorly. The liver was large and tender. The chest plate showed fluid over the diaphragm and stool examination revealed amebae. Thus the diagnosis of amebic liver abscess with involvement of the pleura was established.



Fig. 2.—Extensive pleural effusion.

This case shows the extensive development of fluid which may occur and its rapid recession under emetine. The ease with which such a condition may be confused with pleurisy with effusion and a tuberculous enteritis is obvious.

Case III.—J. P., presenting hemoptysis and findings of pulmonary tuberculosis.

History—On May 29, 1934, a woman, twenty-six years old, came to the out-patient dispensary complaining of a cough with hemoptysis. During the

preceding November while in New York she had had a severe headache, pain down her spine and legs and generalized aching. Her temperature varied from 102° to 103° F. for two weeks. Between November and March the patient remained a semi-invalid. She was sick, lacked strength, suffered from indefinite pains. She often felt chilly. She did not consult a physician and so her temperature was not taken. There was no cough and no diarrhea. Her appetite was poor, weight subnormal and her strength did not permit her working. In March she had a severe pain in the right lower chest aggravated by deep breathing. A cough then developed during which considerable phlegm was raised.

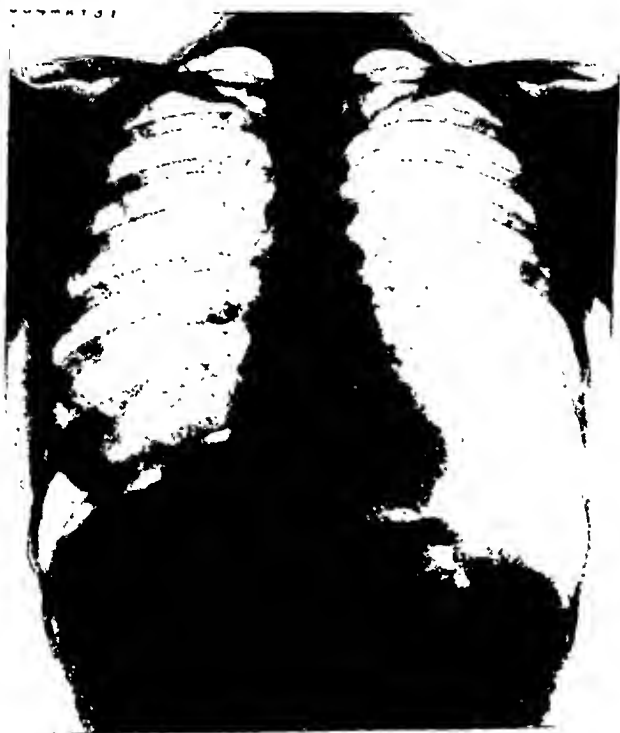


Fig. 3.—Roentgenologic diagnosis, right basilar tuberculosis.

For three weeks the patient expectorated about $\frac{1}{2}$ pint of bloody sputum per twenty-four hours. The hemoptysis began at 4.30 A. M. with a sudden gush of blood followed by high fever. At this time a private doctor was called. He put her in a hospital where she stayed for five days then left because she was financially unable to remain. The x-rays at this time showed pneumonia of the right lower lobe. The doctor suspected tuberculosis although the sputum gave negative tests. In March the patient came to Chicago by bus. Our dispensary doctor suggested three diagnoses: lung abscess, empyema with bronchial fistula, or tuberculosis.

On March 31, 1934, J. P. was admitted to the research hospital on the surgical service of Dr. W. Van Hazel. At this time her temperature was 99.8° F., pulse 120, blood pressure 124/78. Her weight was 13 pounds below normal. The cough and expectoration of blood sputum continued. Examination showed the chest thin, with diminished expansion and decreased tactile fremitus at the right base. There was also dullness and diminished breath sounds and decreased vocal fremitus over this area. No râles were heard



Fig. 4 Resolution of basilar lesion under emetine. Phrenico-exeresis and pneumothorax ineffectual.

Figure 5 taken on admission date showed irregular densities above the right diaphragm and in the region of the second interspace. The findings were consistent with pulmonary tuberculosis. The impression at this time was pulmonary tuberculosis with fluid and thickened pleura at right base. However, nonspecific inflammatory process could not be ruled out.

On June 12, 1934, a right phrenico-exeresis was performed removing the entire length of the nerve. A cervical gland was also removed and sent to the laboratory. The pathologic report was chronic lymphadenitis. A transfusion

was given June 13, 1934. From June 1 to June 21, 1934, 17 sputum examinations were made for acid-fast organisms. Only three times, on June 5, 14 and 20, were such organisms reported. The patient was discharged on June 21, 1934. Her condition was improved but the cough still persisted.

The patient did not make proper progress so was readmitted to the hospital on August 30, 1934. Pneumothorax was performed three different times—August 31, 1934, September 2, 1934, and September 8, 1934. On September 8, 1934, for the first time a diarrhea was noted. This persisted for several days. A transfusion was given on September 10, 1934. On September 13, 1934, a proctoscopy demonstrated lesions typical of amebic ulcers. *Endamoeba histolytica* trophozoites were found in the feces on September 14, 1934, and September 15, 1934. The following day emetine hydrochloride therapy was instituted which was followed by a course of chiniofon. Almost immediate improvement was shown following the administration of the emetine hydrochloride. The improvement in the chest condition was so striking that one of the residents raised the question of the value of emetine as a remedial agent in pulmonary tuberculosis. The patient was tapped on September 18, 1934, but no fluid was found in the chest. By September 24, 1934, the amount of sputum had decreased and was free from blood. The temperature at this time was normal. Figure 4 shows the condition after the phrenico-exeresis, pneumothorax, and treatment with the emetine. Complement fixation for amebiasis showed strongly on October 13, 1934. A proctoscopy was repeated on October 16, 1935, and the colon was found to be free from ulcers. Stools were negative for amebae on three examinations—October 11, 1934, October 12, 1934, and April 18, 1935. From August 31, 1934, to November 16, 1934, 11 examinations for tuberculosis bacilli were made. Only once, September 4, 1934, were acid-fast organisms found. The diagnosis of pulmonary tuberculosis seemed to be so thoroughly justified that pneumothorax was continued for six weeks after the diagnosis of amebiasis was established. The amebic dysentery was regarded as an accidental infection occurring in a patient suffering from pulmonary tuberculosis. The blood picture showed the following changes:

	Hemoglobin	Red blood corpuscles	White blood corpuscles
6/ 1/34.....	50 per cent	3,250,000	7,900
8/30/34.....	53 per cent	3,590,000	16,100
11/13/34.....	6.8 Gm.	4,470,000	13,400

The final hospital diagnosis was amebic dysentery, amebic abscess of the right lung, and questionable tuberculosis. The patient was discharged on November 16, 1934. She was apparently cured of both the dysentery and the lung abscess. After discharge the patient gradually recovered her strength. She was employed as a waitress for some time, often working fourteen hours per day. She has had a major abdominal operation. At present she is married and employed in a position which requires eight hours' work per day. She has not had a pneumothorax since leaving the hospital and has not followed a rest régime. Figure 5, taken July 28, 1937, two and one-half years after discharge, shows only a healed tuberculous area. It is quite clear that the basilar process in the

lung was not due to tuberculosis, but was to be attributed to the rupture of the liver abscess into a bronchus.

Comment.—The history and findings of this case all pointed to tuberculosis. There was a lesion involving the pleura in the upper right lobe diagnostic of tuberculosis. The x-ray findings in the lower lobe were in keeping with a basilar tuberculous process. Acid-fast organisms had been found in the sputum



Fig. 5.—Ancient tuberculous scar, upper lobe. Normal markings, lower lobe.

on 4 occasions. There was persistent hemoptysis. However, the patient did not improve on accepted treatment for tuberculosis: bed rest, phrenico-exeresis, and pneumothorax. Finally amebiasis was diagnosed from stool examination. Treatment was instituted, the patient recovered, and has remained well for two and one-half years. The present chest plate shows only a healed tuberculous area in the right upper lobe.

Case IV.—R. D., presenting history of hemoptysis and periodic evacuations of rather large quantities of bloody fluid.

History.—On July 23, 1936, a man, twenty years old, came to the enterologic clinic of the out-patient dispensary complaining of hemoptysis and pain in the right side. On the same day he was admitted to the research hospital on the service of Dr. P. H. Holinger for a bronchoscopy. The history revealed that during the preceding January he had lost weight and was feeling tired, which was attributed to an attempt to work and attend school simultaneously. On February 9, 1936, he caught cold which was complicated by



Fig. 6.—Roentgenologic diagnosis: bronchiectasis with pleural involvement

pleurisy and pneumonia in the right lower lobe. His temperature remained about 102° F. for two weeks. His physician kept him in bed eight weeks. While at home he was tapped and a wine glass of clear fluid was removed from the chest. x-Ray plate showed "a spot on the lower right lung and pleurisy." About the middle of May he felt a sense of fulness below the right costal margin, and at this time he began to expectorate about 2 cups full of bloody sputum every twenty-four hours. This lasted three days. After this he felt better and became ambulatory. In discussing his case in retrospect the patient recalls that he usually experienced this sense of fulness just prior to periods in

which he coughed up considerable material. After such periods of evacuation the sensation of fulness was relieved. A month later he had a relapse and was again ordered to bed. The last of June he coughed up about 2 quarts of bloody material. He was then sent to the Municipal Tuberculosis Hospital where bronchoscopies and sputum tests were done. All specimens were found negative for tubercle bacilli. At this time the patient was about 15 pounds below his normal weight.



Fig. 7. Right pneumothorax and phrenico-exeresis. Ineffectual in preventing hemoptysis.

Bronchoscopies x-rays and lipiodol tests were done at the research hospital. The bronchoscopic report of July 25, 1936, showed that a large quantity of mucopurulent secretion was aspirated and that this was followed by bleeding. The mucosa was red and slightly ulcerated. The right bronchus only was involved.

The x-ray plate of chest (Fig. 6) taken July 24, 1936, showed that the right diaphragm was elevated and there was a dense area above it. The fluoroscopic studies showed that the respiratory excursion of the diaphragm was

limited and that there was an appreciable involvement of the pleura. It was concluded that the findings were consistent with a bronchiectasis with pleural involvement. Later plates were made after lipiodol instillation failed to show any significant bronchial dilatation. Smears from the sputum made on July 25, 1936, and July 27, 1936, did not show acid-fast organisms. The patient was discharged from the hospital on August 30, 1936. Two possible diagnoses were still considered: thickened right lower pleura with pleurisy (tuberculous basis) and bronchiectasis.



Fig. 8.—Amebic abscess discharging into bronchus.

In October, 1936, R. D. developed poliomyelitis of the right shoulder. This was cared for at the Municipal Contagious Hospital and the orthopedic department of the Research Hospital. During the period in which he was confined to bed in the Contagious Hospital the sputum ceased almost entirely. When he became active and returned to the orthopedic dispensary the sputum returned. It was thus necessary to hospitalize him again on December 28, 1936. Further bronchoscopies and x-rays gave essentially the same findings. In January, 1937, the enterologic department transferred the case to the medical

dispensary. Complete history and examination revealed findings similar to those of the other departments. The diagnosis was given as hemoptysis following pleural effusion presumably on a tuberculous basis although physical evidence of tuberculosis was lacking.

He was again admitted to the surgical department of the hospital on April 9, 1937, on the service of Dr. W. Van Hazel. From April 17, 1937, to May 19, 1937, 11 bacteriologic examinations of sputum were made. No acid-fast organisms were found. Previously at least 10 smears had been examined by the dispensary laboratory, all of which were negative for tubercle bacilli. On April



Fig. 9.—Recovery almost complete.

17, 1937, a right phrenico-exeresis was performed. Figure 7 shows the result of this. On April 24, 1937, there occurred a profuse expectorating of bright red blood at 10 P. M. The patient felt better following this. Pneumothorax was done on May 1. Figure 8 taken on May 8, 1937, shows the right lung partially collapsed and fluid in the chest cavity.

From this x-ray Dr. Van Hazel decided that there was a perforation from the liver through the diaphragm into the bronchus. Amebic abscess being suspected the patient was questioned specifically about previous attacks of diarrhea. It was then learned for the first time that he had had amebic dysentery follow-

ing drinking some water at the stock yards fire in 1934. At that time he had been treated with emetine hydrochloride and had forgotten the whole incident. He was then sent to the laboratory and on May 15, 1937, mobile trophozoites of *Endamoeba histolytica* were isolated from the sputum. The final diagnosis was then made of amebic abscess of the liver that had ruptured through the diaphragm and drained through the bronchial tree. The rupture most certainly occurred at the time of the "pneumonia" in 1936. Emetine hydrochloride therapy was instituted and the patient showed immediate response. Following this a course of chiniofon was given. The proctoscopic findings were negative. On June 8, 1937, the patient was discharged in very good condition. Figure 9, taken two and one-half months after final discharge, shows elevation of the right diaphragm, which of course is due to the phrenico-exeresis. Localized density near the right lateral chest may represent residual change of previous pathologic process.

Comment.—In this case an acceptable diagnosis was not reached for nearly three years. The case was considered to be due to bronchiectasis because of repeated hemorrhage with no evidence of tuberculosis given by x-ray or sputum examination. The patient was so treated for one year by repeated bronchial aspirations. As this brought no improvement the diagnosis of tuberculosis was adopted. In keeping with this, a right phrenico-exeresis and pneumothorax were done. After these, a profuse hemoptysis occurred. On examination of Fig. 8 the surgeon noted an area of rarefaction below the diaphragm. On questioning, the patient for the first time volunteered the information of a previous attack of amebic dysentery. Sputum examination revealed amebae. With administration of emetine hydrochloride the patient recovered.

Case V.—J. G., presenting subdiaphragmatic abscess with multilobar empyema.

History.—An emaciated, critically ill man, thirty-five years old, was admitted to the hospital on August 6, 1934. He had been well until May 21, 1934, when a bloody diarrhea started. He had 10 to 15 stools per day. There was constant abdominal pain and fever. As his condition did not improve with bed rest a private physician was called about June 15th. The doctor sent him to a hospital where he remained eight days and was then sent home with the condition undiagnosed. At this time a pain developed over the lower ribs in the midsternal line and radiated to the lumbosacral region, extending into the extremities.

About August 1st the pain localized in the right costal margin. Examination of the lungs showed diminished breath sounds and dullness in the base of the left lung posteriorly. Marked tenderness was evident in both upper quadrants of the abdomen with moderate rigidity. The impression was a subdiaphragmatic

ragmatic abscess, possibly on an amebic basis. A history was obtained of drinking water at the stock yards fire several days before the onset of the diarrhea. Because of this, complement fixation tests were made for typhoid, paratyphoid A and B, and undulant fever. All of these were negative. Proctoscopy revealed a somewhat inflamed mucosa but no ulceration in the 20 cm. examined. Stools were examined but no parasites were found. The whole condition gradually became aggravated. Blood transfusions were given on August 23, 1934, and August 25, 1934. There was a considerable general reaction to the second transfusion. At this time there was a bloody stool passed in which were found active trophozoites of *Endamoeba histolytica*. The diagnosis was then definitely made of amebic dysentery, amebic subdiaphragmatic abscess and pleural involvement. The patient was put on treatment and the liver abscess which was on the right side was drained. The chest was tapped on the left side September 18, 1934, and September 23, 1934, removing yellow pus in amounts of 1000 cc. and 250 cc. respectively. The first fluid encountered was thin and contained only a moderate number of pus cells. As the exploring needle was probed deeper a thick, viscid pus was encountered. This was interpreted as meaning that the first fluid arose from the pleural cavity and represented fluid in process of transformation into the pus of empyema. The second fluid was evidently obtained after the needle passed through the diaphragm into a liver abscess, subdiaphragmatic in location. Several more transfusions were given but all were ineffectual. The patient expired September 28, 1934. The postmortem revealed multiple amebic abscesses of the liver in addition to the large one in the right lobe which had been drained. There was a large abscess beneath the left diaphragm and extensive adhesions binding the left pleura to the diaphragm. These contained pocketed fluid giving rise to a multilocular empyema with pus of varying consistencies.

Comment.—Shortly after the entrance into the hospital it was possible to make a diagnosis of liver or subphrenic abscess. It was twenty-one days later before we were able to isolate the amebae from the stools. Fluid which could be recognized by x-ray appeared about the diaphragm rather late in the course of the case. However, the autopsy showed fairly extensive adhesions with many pockets containing fluid. This would indicate that a fibrinous pleurisy may precede one in which fluid is an outstanding manifestation.

DISCUSSION

From these cases one may visualize the pathogenesis of the pulmonary involvement fairly clearly. The involvement is by extension. The abscess reaches the diaphragm from below and pleurisy appears above. The inflammatory reaction may take the form of a severe pleural reaction with fluid formation. The

fluid may be sufficient in amount to fill the chest cavity (Case II, Fig. 2). At another time the fluid may be small in amount and the fibrinous exudate attaches the lung to the diaphragm. This was the course of events in Cases III and IV. The fibrinous reaction may continue and be replaced by an extensive sclerosing process as in Case V. As the condition progresses the adhesions become more extensive and the abscess ruptures into the lung establishing a communication with a bronchus. When the x-ray plate is taken and the physical examination is made at this stage, a diagnosis of bronchopneumonia will be warranted. The x-ray plate will show a shadow compatible with such a diagnosis and the physical findings (dulness, bronchial breathing, increased fremitus) will indicate a consolidation.

When the patient is seen at a later stage after there has been an expectoration of much of the material flooding the dependent bronchi the picture is different. The bronchial markings will now be discernible. They will be increased and thickened. The picture will be one usually seen in peribronchiolar involvement. The condition will be confused with a basilar tuberculosis or a bronchiectasis. The persistent recurrence of a bloody sputum will doubtless favor a diagnosis of tuberculosis. It is interesting to note that Case III first came under observation at the Research Hospital at this stage. The pneumonia picture appeared two months prior to admission. In her case a diagnosis of tuberculosis was made and treatment for this instituted. Case IV entered the hospital a somewhat longer time after his pneumonic episode. In his case the preponderance of findings did not indicate so clearly tuberculosis and so a diagnosis of bronchiectasis was made. When he did not recover under treatment for bronchiectasis then the alternate diagnosis of tuberculosis was adopted.

If the inflammatory reaction proceeds more slowly, then the fibrous tissue reaction occurs and fluid appears later. If the condition remains undiagnosed a sufficient time the fluid will inevitably be changed into pus as in Case V.

From a study of these cases one is struck by the long time which a patient may tolerate amebic infections of the liver and yet experience a complete recovery. The time between symptoms of liver involvement and treatment was in Case I, three

years; Case II, three weeks; Case III, eleven months; Case IV, fifteen months and Case V, two months. The apparent fair state of health presented by Cases III and IV is doubtless due to the establishment of drainage of the abscess. The amebae cause very little permanent damage to lung tissue. After they have been destroyed by emetine the tissue rapidly returns to normal. This has been known for some time with reference to the liver. It is further interesting to note that even during the height of the involvement of the lung (Case IV) there was no significant ulcerations to be seen through the bronchoscope and the bronchial tree as visualized by the lipiodol instillation was normal. One may raise the question as to whether the amebae are viable in the lung. The organisms recovered from the sputum were normal in appearance and motility. The reports of Craig also substantiate their viability.

The authors wish to thank Dr. Willard Van Hazel for the privilege of reporting Cases III and IV which were seen in consultation prior to their transfer to the medical service. They wish to thank Dr. P. H. Holinger for the use of his bronchoscopic records in Case IV.

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THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF PNEUMONIA

THE DIAGNOSIS OF PNEUMONIA

THE existence of a pneumonic consolidation of the lung usually is readily recognized. The diagnosis of lobar pneumonia, however, entails more than the mere demonstration of a pneumonic consolidation. It involves also the identification of the bacterial incitant and the consideration of factors which influence the course and outcome of the disease. Every case of acute pulmonary involvement demands scrutiny from anatomic, etiologic and prognostic viewpoints.

The Anatomic Diagnosis.—The most valuable early diagnostic signs of pneumonia is the suspicion that it might be present. This suspicion is aroused, even in the laity, in the illustrative case with the well-known picture of the sudden onset of illness with an actual chill, rapidly mounting fever, shallow, restrained respiration, pain in the chest and followed by cough with expectoration of rusty sputum. If in such a case we follow the imploration of Austin Flint and "employ physical exploration" and find the classical signs of localized consolidation the diagnosis of the existence of pneumonia is at once established. It is common medical knowledge, however, that not always does pneumonia announce itself with such a conspicuous parade of distinctive marks. Difficulties arise in diagnosis because of the variability of the presenting symptoms, or the delayed display of the signs of consolidation. Diversity in the mode of presentation accounts for about half of the deferred diagnoses. These alterations in symptomatology may be

grouped according to the manner in which they obscure the clinical picture:

1. Gradual onset, developing in the course of an upper respiratory infection.

2. Sudden onset of illness with exaggerated symptoms such as pain, meningismus or delirium.

3. Development, gradual or sudden, in the course of other illness such as congestive heart failure, undulant fever, or delirium tremens, which masks the pneumonia.

4. Silent onset—without symptoms pointing to pulmonary involvement, commonly seen as “walking pneumonia.”

The physical findings which establish the diagnosis of pneumonia are those of consolidation, viz.: decreased mobility of the affected side of the chest, increased tactile fremitus, diminished resonance to dullness, tubular breathing and bronchophony. These findings may not occur for from three to five days and if waited for, valuable therapeutic time is lost. The earlier physical findings occur during the stage of engorgement before solidification is present. At this stage the appearance of the patient bears almost as much diagnostic weight as do the often meager signs. The “pungent heat of the body,” the flushed face, the herpes about the lips, the increased respiration rate with the “expiratory grunt” all contribute to this appearance of illness. There may be some limitation of respiratory motion, the percussion note is more resonant and may possess a tympanitic quality. The breath sounds are suppressed and only gradually become blowing in character. The voice sounds become altered only as consolidation progresses. These early changes in signs are comparative and can best be elicited with the patient sitting in bed, a procedure condoned early, but condemned later. One of the earliest positive signs is the development of whispered bronchophony. This can be educed long before changes in the spoken voice can be detected. The crepitant *râle* of Laënnec appears early and is almost pathognomonic of pneumonic consolidation. It may only be confused with the crepitant friction rub. These crepitant sounds have been promiscuously described and have been likened to sounds produced both by rubbing the hairs close to the ears or by throwing granulated sugar on an open fire. If the acoustic differentiation is to be made the *râle* resembles

more the creaking of the hair while the rub is similar to the crepitation of the sugar. The distinction between these sounds is of more than academic interest because the rub is frequently heard in the absence of pneumonitis. Early too, at the site of the pleuritic pain the typical coarse friction rub may be detected, but usually the pain is so intense that the patient will restrain his breathing so effectively that no rub is heard. A striking diagnostic feature, as well as an early one in physical exploration is the rapid change in the findings, so that in a few hours the entire picture may be metamorphosed.

The respiration in pneumonia is characteristic. It is rapid, restrained and shallow. The respiratory rate is increased twofold or even threefold. With the average febrile increase in the pulse rate, the pulse-respiration ratio is disturbed so that instead of the normal 4 to 1 ratio it may be 2 to 1 or even $1\frac{1}{2}$ to 1. The very great early differential value of this sign is too often underestimated.

Not infrequently the physical findings are confusing. In such cases it is being more and more appreciated that for definite confirmation of the diagnosis roentgen ray is indispensable. Ordway¹ enthusiastically proclaims the value of the x-ray film in the demonstration of pneumonia before the characteristic physical findings appear. It is not at all uncommon to be astounded by the paucity of findings in the presence of extensive involvement as demonstrated by the x-ray film. Roentgen study serves a dual purpose, in establishing the existence and location of pneumonic infiltration and also in excluding other intrathoracic pathology which might be confused with it.

The clinical picture, physical signs and x-ray merely establish the presence of pneumonic consolidation. Such consolidation can be caused by a variety of immunologically different strains of pneumococci as well as by other organisms. While there is some difference in these various pneumonias, chiefly in the degree of toxemia and in the statistical mortality, this difference cannot be recognized on purely clinical evidence. The bacterial incitant can be identified only by bacteriologic means. Therefore, the diagnosis of pneumonia does not rest with merely establishing the existence of the disease but demands the identification of the particular responsible organ-

ism. To this end studies of the sputum are mandatory. Even the microscopic examination of the stained smear yields important information. The demonstration of large numbers of pneumococci in the sputum both intracellular and extracellular is expected in pneumonia; the absence of these organisms in the sputum of a suspected case would certainly cast well-founded doubt on the diagnosis. The recognition of the particular type of pneumococcus is also of prime importance from the standpoint of establishing the presence of pneumococcus pneumonia, instituting specific therapy and judging prognosis. While pneumococci may be obtained from the mouths of 50 per cent of healthy individuals they are of the types which are least often the cause of the disease. Pneumococci Type I and Type II, which are responsible for over 50 per cent of the cases of pneumonia, are seldom found in healthy individuals other than contacts (Irons²). Typing gives both information necessary for the use of the specific sera of Types I and Types II, and in addition it lends a notion as to the average prognosis. For example, Type III pneumonia is a different disease prognostically than either Type I or Type II. Faced with the knowledge that we are dealing with a Type III infection with an average mortality of 50 per cent, heroic therapeutic means such as oxygen therapy and intravenous glucose medication should be instituted immediately rather than as a measure of last resort. The etiologic diagnosis also reveals occasionally the presence of other causative organisms such as streptococci, staphylococci, Friedländer's bacillus and *Bacillus abortus*. While no specific treatment exists for these infections the accumulation of statistics as to the frequency of their occurrence leads to information which will eventually be important in their control. The establishment of the streptococcus as the cause of a pneumonia is an indication for the trial of sulfanilamide as a therapeutic agent.

The Diagnosis from the Standpoint of Prognosis.—The diagnosis to be complete should also include the evaluation of other factors which influence the outcome. These are, in addition to the determination of the type of pneumococcus, the location and extent of involvement, the degree of toxemia, the response of the individual and the presence of untoward conditions which magnify the risk.

Location and Extent of Involvement.—The mortality is greatly influenced by involvement of more than one lobe, and still greater when the involvement is bilateral. The location of the pneumonia in the upper lobes is more serious than in the lower lobes, and the left upper lobe pneumonia, regardless of type, carries with it the most serious outlook. It is a distinct surprise to see recovery take place in left upper lobe pneumonia.

Toxemia.—The degree of toxemia may be measured to some extent by blood culture. While there probably is a bacteremia present at some time in every case, its determination is possible only in the cases of extensive or persistent invasion of the blood stream. Positive blood cultures indicate an overwhelming of the resistance of the individual. Cole³ has demonstrated that when the blood cultures were positive the mortality was 67.1 per cent, while in the case of negative culture the mortality was 11.6 per cent.

The degree of toxemia is to some extent reflected in the serum bilirubin. All cases of pneumonia develop an elevation of the serum bilirubin, due to the inability of the anoxic liver cells to excrete the excessively formed bilirubin. Some cases, due to actual necrosis of liver cells, develop frank choluric jaundice. These cases seldom recover. Hence the determination of the degree and the type of icterus is of distinct value.

The response of the patient can be measured to some extent by the blood count. Elevation of the white count occurs within a few hours and persists until after the crisis. In the majority of cases the leukocytosis is between 15,000 and 35,000. This early relatively high white count is an important diagnostic aid. With counts less than 10,000 the diagnosis of lobar pneumonia should be subjected to further diagnostic scrutiny. If the diagnosis is substantiated, the low count indicates deficient defensive powers, mild infection or complication, while counts of over 40,000 indicate strong combative powers in the presence of intense infection.

Other laboratory procedures have been advocated but have not come into common usage. These are the demonstration of the specific precipitin substances in the urine, the absence of urinary chlorides, decreased oxygen content of the blood asso-

ism. To this end studies of the sputum are mandatory. Even the microscopic examination of the stained smear yields important information. The demonstration of large numbers of pneumococci in the sputum both intracellular and extracellular is expected in pneumonia; the absence of these organisms in the sputum of a suspected case would certainly cast well-founded doubt on the diagnosis. The recognition of the particular type of pneumococcus is also of prime importance from the standpoint of establishing the presence of pneumococcus pneumonia, instituting specific therapy and judging prognosis. While pneumococci may be obtained from the mouths of 50 per cent of healthy individuals they are of the types which are least often the cause of the disease. Pneumococci Type I and Type II, which are responsible for over 50 per cent of the cases of pneumonia, are seldom found in healthy individuals other than contacts (Irons²). Typing gives both information necessary for the use of the specific sera of Types I and Types II, and in addition it lends a notion as to the average prognosis. For example, Type III pneumonia is a different disease prognostically than either Type I or Type II. Faced with the knowledge that we are dealing with a Type III infection with an average mortality of 50 per cent, heroic therapeutic means such as oxygen therapy and intravenous glucose medication should be instituted immediately rather than as a measure of last resort. The etiologic diagnosis also reveals occasionally the presence of other causative organisms such as streptococci, staphylococci, Friedländer's bacillus and *Bacillus abortus*. While no specific treatment exists for these infections the accumulation of statistics as to the frequency of their occurrence leads to information which will eventually be important in their control. The establishment of the streptococcus as the cause of a pneumonia is an indication for the trial of sulfanilamide as a therapeutic agent.

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Other laboratory procedures have been advocated but have not come into common usage. These are the demonstration of the specific precipitin substances in the urine, the absence of urinary chlorides, decreased oxygen content of the blood asso-

ciated with increased carbon dioxide and the little understood Takata-Ara test and Weltman reaction.

UNTOWARD CONDITIONS WHICH INFLUENCE THE OUTCOME

The presence of other maladies such as diabetes, nephritis or heart disease must be considered as a part of the diagnosis of pneumonia because of the influence borne to therapy as well as to the seriousness imparted to prognosis. Alcoholism, starvation and exposure must be clinically appraised in relation to the diagnosis. These conditions, chiefly alcoholism, are notoriously associated with pneumonia, conceal its presence and augment the mortality.

THE DIFFERENTIAL DIAGNOSIS

The differential diagnosis considered in relation to these same variations from the typical picture includes the following conditions:

(A) Similarity of onset.

1. Upper respiratory infection.
2. Other forms of pneumonia.
3. Tuberculous pneumonia.

(B) Pneumonia with exaggerated symptoms.

1. Meningitis.
2. Abdominal pain.
3. Delirium tremens.

(C) Confusing physical finding.

1. Pleurisy with effusion.
2. Pulmonary infarction.
3. Pulmonary congestion.
4. Massive collapse of the lung.
5. Acute pericarditis.

SIMILARITY OF ONSET

The Upper Respiratory Infection.—The upper respiratory infection by its similarity of onset with fever, prostration, cough and pleuritic pain presents a picture which is in no wise different from the onset of pneumonia. In a given case one may be hard put to say whether or not there will be a pneumonia. This is true in a light of the fact that 30 per cent of the cases of pneumonia are preceded by an upper respiratory

infection which has been present from four to fourteen days. Pneumonia is suggested if instead of the usual prompt recovery the patient progressively becomes worse, the fever higher, the cough more severe, the sputum bloody and the pulse-respiration ratio disturbed. Frequently in these cases it is difficult to say whether the pneumonia is a complication or the "cold" is in reality a gradual onset of pneumonia. Of particular value in these cases is the examination of the sputum and where Type I or Type II pneumococci found the diagnosis of early pneumonia made and treatment instituted accordingly. Roentgen studies in the persisting "cold" will only too often reveal pneumonia.

Other Forms of Pneumonia.—Bronchopneumonia in adults is as a rule a secondary event due to the extension of infection of the upper respiratory tract or as the result of aspiration of infective material in the presence of debilitation from prostrating disease such as nephritis, carcinoma, etc. In these cases the general condition of the patient leads to its diagnosis rather than physical signs. Elevation of temperature, cough and purulent expectoration, leukocytosis and crepitant râles at the bases intimate its presence. In the rare primary form in adults, with a diffuse bilateral involvement there are found scattered areas of consolidation with crepitant râles heard over the entire chest. Even in the "confluent" type the findings are never so definite as in lobar pneumonia. In many cases the differentiation is a matter of opinion.

Acute Tuberculous Pneumonia.—Acute tuberculous pneumonia not infrequently presents an identical onset with that of lobar pneumonia, with chill, chest pain, cough, and bloody expectoration and physical findings of consolidation. Aid to differentiation are the history of previous ill health, with hemoptysis or pleurisy, persistent bloody expectoration, moderate leukocytosis, recurring chills and relatively few pneumococci in the sputum. The diagnosis is eventually established by roentgen ray and the demonstration of the tubercle bacillus in the sputum. When pneumonia involves the upper lobe, particularly the right, it frequently must be distinguished from tuberculous pneumonia. The loud blowing tubular breathing in Mohrenheim's fossa bears close resemblance to amphoric breathing and often is considered as representing cavitation.

PNEUMONIA PRESENTING EXAGGERATED SYMPTOMS

Meningitis.—Meningitis may be suspected when pneumonia presents itself with marked cerebral symptoms and meningismus. In such cases there is question whether the symptoms are due to an epidemic meningitis or pneumococcus invasion of the meninges. Meningeal symptoms occurring after the development of the pneumonia practically always indicate pneumococcus meningitis. With meningismus the signs of meningeal irritation are never so definite as in meningitis. In any suspicious cases lumbar puncture should unhesitatingly be employed. By this procedure the diagnosis is seldom long in doubt, the spinal fluid examination revealing purulent fluid with the causative organism in meningitis, and clear fluid in meningismus.

Appendicitis.—In pneumonia the pleuritic pain when referred to the right lower quadrant begins there, while in appendicitis it is at first diffuse and then localizes in the region of McBurney's point. Such lower abdominal pain being in reality pleuritic in origin is associated with restrained breathing and suppressed breath sounds. The greatest difficulty in the differentiation is in the fact that because of the acuity of the abdominal condition the pneumonia is not suspected and therefore sought. This is especially true in children. Of particular diagnostic import is the alteration of the pulse-respiration ratio. In all such doubtful cases x-ray will establish the diagnosis and forestall operation.

Perforated ulcer is diagnosticated by a careful and exacting history revealing a periodic postprandial pyrosis (Singer¹), sudden onset of intense pain in the epigastrium with cramp-like exacerbations, localized tenderness and varying degrees of shock. If there is a free perforation into the peritoneal cavity there will be added the characteristic board-like rigidity and pneumoperitoneum, which may be absent in the subacute, walled-off perforation.

Delirium Tremens.—Delirium tremens resembles lobar pneumonia in many ways. Both develop frequently in alcoholics, both have a sudden onset following exposure, there is the same rapid development of the appearance of ill health, with flushed face, profuse sweating, rapid respiration and fast pulse. All patients with pneumonia develop delirium and many

patients with delirium tremens develop pneumonia. In delirium tremens the delirium is present at the onset, the disorientation is for time, place and person, there is marked apprehension, coarse tremor and bizarre visual illusions and hallucinations. In pneumonia the delirium usually develops later and the orientation for person is retained. However, either may be a complication of the other.

CONFUSING PHYSICAL FINDINGS

Pleurisy with Effusion.—The onset of pleurisy with effusion is usually gradual with pleuritic pain, but may be sudden following some exposure. The pain does not subside as it usually does in fibrinous pleuritis. After the fluid accumulates the findings are distinctive, with limitation of motion, decreased tactile fremitus, diminution of resonance to flatness, displacement of the heart to the opposite side, suppressed breathing or distant bronchial breathing, decreased vocal fremitus or distant bronchophony. In any doubtful case the diagnosis is readily established by a well directed aspiration needle. In addition, a roentgen examination gives conclusive differential information.

Pulmonary Infarction.—Pulmonary infarction closely resembles lobar pneumonia because of similarity of onset, symptoms and physical findings. Distinction between the two is made on the presence of concomitant conditions giving rise to the embolus, such as heart conditions, particularly rapid auricular fibrillation with acute failure, or endocarditis; sepsis, puerperal or otherwise; crushing injuries, etc. The sputum is more likely to be frankly bloody, there are fewer organisms, the blood culture is negative and jaundice occurs early.

Pulmonary Congestion.—Active pulmonary congestion occurs after trauma to the chest with or without fracture of the ribs. There is marked dyspnea, pain at the site of injury and on physical examination diffuse sibilant and mucous râles are present. There are no alterations in resonance, breath or voice sounds. Usually the signs disappear in a day or two.

Passive congestion of the lungs is distinguished by the history, the bilateral involvement of the bases posteriorly, the diffuse, coarse, moist râles and the absence of signs of consolidation. Roentgen ray shows a diffuse clouding of the bases

of both lungs. The sputum reveals many "heart failure cells" and few pneumococci.

Massive Collapse of the Lung.—In massive collapse there is a history of operation, or trauma to the chest, with the characteristic pulling of the mediastinal structures to the affected side, its retraction, the narrowing of the intercostal spaces, the elevation of the diaphragm and the relative silence of the chest.

Acute Pericarditis.—In acute pericarditis the febrile onset, with dyspnea, pain in the chest, cough and physical findings of compression of the lung posteriorly (Bamberger's sign) leads to confusion with left lower lobe pneumonia. The distinction is made on the history of preceding rheumatic infection, the exaggerated dyspnea, the characteristic enlargement of the area of cardiac dullness at the base of the heart, the pulsus paradoxus and the alterations in the electrocardiogram. The diagnosis is established by the typical cardiac shadow on the roentgen film.

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CLINIC OF DR. ARTHUR H. PARMELEE

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THE DIFFERENTIAL DIAGNOSIS OF PNEUMONIA IN CHILDHOOD

PNEUMONIA in adults is frequently difficult to diagnose, because of the variations in the clinical picture presented. In children, the difficulties of diagnoses are even greater, because of certain physiologic and anatomic peculiarities present in the growing organism which make the reactions to the infection different. Subjective symptoms as well as physical findings are often quite different in children from those in adults. We also recognize marked differences in the young infant, as compared to older children.

The term "pneumonia" is a broad one including a variety of pathologic changes in the lungs, as well as varying etiologic factors. Not all pneumonias are due to the pneumococcus, of which there are, as you know, many types; some are streptococcus infections, and some are due to the influenza bacillus. Thus, when we say a child has pneumonia, the diagnosis is not complete unless we know approximately the pathologic changes present in the lungs, and the causative organism. It is impossible to discuss in this clinic all varieties of pneumonia, but I can show you a few cases exemplifying some of the more common clinical pictures, and discuss the problems in diagnosis which they present.

Case I.—This four-year-old boy was well until six days ago, when he complained of being chilly about 4 o'clock in the afternoon, and acted tired and peevish. He did not care for any supper, and went to bed complaining of stomach ache. Thirty minutes later, he complained of severe pain in the right side of his abdomen, and he vomited. The mother took his temperature and found it to be 103° F. I saw him soon after that, and could find nothing on physical examination to account for his symptoms. There was some general abdominal tenderness, but no rigidity and no localized tenderness. His lungs seemed entirely clear. He looked and acted sicker than he should with the

usual febrile disturbances due to upper respiratory tract infections which are prevalent at the present time. On the following day, his temperature remained between 103° and 104° F. all day, and he continued to complain of pain in the right side of his abdomen. He was very restless and irritable. When seen by me that afternoon, his respirations were rather rapid, and at times there was a short grunt at the beginning of expiration. His abdomen was soft, and there was no localized area of tenderness. I was still unable to find any physical findings of pneumonia, although I was quite suspicious of it by now, because of the rapid breathing, the expiratory grunt, and the sustained temperature elevation. On the third day of his illness, I was able to hear a pleural friction rub in the right axilla, and diminished breath sounds over the right lower lobe, as well as a relative decrease in resonance over this area. Since then the physical findings have become typically those of a frank lobar pneumonia of the right lower lobe with pleuritis more marked than in the average case. His temperature curve has remained almost flat at 103° to 104° F. until this morning, when it dropped to 101° F., but is now up again to 104.6° F. His right lower lobe is now very dull to percussion, one hears loud bronchial breathing over this entire area, and there are numerous crepitant and sub-crepitant râles with here and there some moist râles.

This case represents primary lobar pneumonia in a form quite typical of the disease in childhood. Some features of this case deserve discussion. Vomiting is a symptom of onset in nearly any acute febrile disturbance in childhood. This is a response to the invasion of an infectious disease which is peculiar to childhood. Another symptom of onset not infrequently seen in childhood, though not present in this case, is convulsions. When convulsions occur as a symptom of onset, there is usually no recurrence of convulsions later in the course of the disease, except as might be due to some complication involving the central nervous system. A peculiar short grunty sound made by a child at the beginning of each expiration is, in my experience, almost pathognomonic of pneumonia. It is due to pain produced by the pleurisy. Inspiration after reaching a certain point is stopped abruptly, and the grunty noise precedes the expiratory movement. In certain cases of peritonitis, one may encounter this same symptom. When, however, the expiratory grunt is due to pain from peritonitis, there is marked restriction of abdominal movement during respiration, most of the respiratory action being thoracic, while just the opposite is true in pneumonia.

There are two other features of this case which deserve mention: one is the early appearance of rather extensive pleurisy which persisted through several days, a feature which makes the experienced clinician suspicious that empyema will complicate the convalescence. The other feature of interest is that this morning the temperature dropped to 101° F., and although it is now up to a very high point again, this morning's drop was the first that has occurred since the onset of the disease. This phenomenon almost always is a signal that a true crisis is only a few hours away.

Case II.—This nine-year-old girl had a common cold three weeks ago with the usual symptoms of rhinitis, pharyngitis, and laryngitis. She had almost no fever during the first three days. On the fourth day, she had a trouble-

some cough, and a fever of 101° F. in the afternoon. I saw her that day, and there were a few scattered coarse moist râles to be heard in various parts of her lungs, but no other chest findings. The following day her temperature, which had been 99° F. in the morning, rose to 102° F. in the late afternoon, and on examination that day, I found a small area of bronchial breathing on both sides at the lower angle of the scapula, and also crepitant râles were heard over these areas at the end of inspiration. She had no pain, and although her respirations were comparatively rapid, they were not labored, and not associated with any expiratory grunt. She did not act very sick, but was rather languid.

On these findings, I made a diagnosis of bronchopneumonia. For the next ten days, she ran a remittent temperature, the low point being about 101° F. in the morning, the peak being 103° to 103.4° F. in the late afternoon or evening. Cough and general fatigue were the outstanding symptoms. The temperature fell gradually after that with the peak being each day a little lower, and the morning remission also reaching a lower point each day. The cough subsided, and she began to take interest in food. Now she has had a normal temperature for two days.

During the first week of her bronchopneumonia, the lung findings increased, some dulness could be elicited in the axilla and over the middle portion of the thorax posteriorly on both sides, with bronchial breathing and moist as well as crepitant râles. Elsewhere in both lungs there were small areas where moist and crepitant râles could be heard. She never had any marked dyspnea, and never any pain or cyanosis.

This case represents a typical uncomplicated bronchopneumonia. We have been having an epidemic of common colds recently, and in other cases of bronchopneumonia I have seen, the course has not been as smooth as in this case. One of the frequent complications which has seriously interfered with convalescence has been otitis media, usually with suppuration. It is important to carefully examine the ears with an otoscope at every visit; you cannot rely on any subjective symptoms to call your attention to the ears. Children localize pain very poorly; they may say they have headache, or not infrequently make no complaint of pain whatever. An unexpected rise in temperature during the course of bronchopneumonia will frequently go unexplained until suddenly one day the mother or nurse finds a purulent discharge from the ear. No physician who treats children should neglect the daily examination of the ears with an otoscope.

Case III.—This girl is two years old. She was entirely well until eight days ago, when she suddenly vomited, her hands and feet were cold and blue, lips pale, and she said she was cold and tired. She was given a warm bath, and put to bed with warm blankets. Two hours later, her temperature was 106° F. When seen at that time, physical examination revealed nothing to account for her illness. The onset with a chill and rapid rise in temperature in a female infant with no physical findings to explain it, gave rise naturally to a strong suspicion of pyelitis. This suspicion was strengthened during the next three days by the character of the temperature curve, which showed the marked remissions and high peaks characteristic of pyelitis. Specimens of urine

were, however, consistently negative. On the fourth day, she was brought to the hospital. Up to this time, daily examinations of the lungs had been made with entirely negative findings, but a roentgenogram of the chest taken when she entered the hospital, showed a dense shadow in the middle portion of the right lung, roughly corresponding to the area of the middle lobe and upper portion of the lower lobe. The following day, signs of consolidation were made out for the first time by percussion and auscultation. By night of the sixth day, her temperature fell to 97° F., and has remained slightly below normal since. At no time was cough, dyspnea, or pain a symptom.

This case illustrates a type of primary pneumonia seen occasionally in children which is impossible to diagnose in the first three or four days without the aid of the x-ray. Chills occur infrequently in infancy and young childhood. When an illness is ushered in by a chill, our first thought is of pyelitis, especially if the child is a female. Pneumonia is the next most probable disease to be thus initiated. Lobar pneumonia usually exhibits a temperature curve that resembles a plateau, but that it may show a markedly fluctuant character with high peaks and deep valleys is illustrated by this case.

Case IV.—I have only the clinical chart of this case to show, since the patient died a few days ago. It was a newborn infant that weighed 6½ pounds at birth, and seemed normal during the first six days of its life. It then began to nurse poorly at the breast, was restless, looked pale and slightly cyanotic at times. In the next three days, it became continuously weaker, lost weight, and had a feeble whining cry. It had no rise in temperature, but the respirations were unusually rapid. Physical examination showed scattered moist and subcrepitant râles throughout the lungs, but no other findings. Death occurred on the twelfth day. At autopsy, there were several rather large areas of confluent bronchopneumonia in both lungs.

I am presenting the clinical record of this case to illustrate a point too frequently ignored or not realized, *i. e.*, that newborn infants will often show no febrile reaction to an infection, and particularly when this infection is very virulent and overwhelming.

Case V.—This, too, is a very young infant; it is six weeks old and has been sick three days. The baby was well until then. His father had been home several days with an attack of influenza, and three days ago the baby developed a stuffy nose, and a cough, and slight fever. The cough became rapidly worse; it was almost continuous, and did not permit the baby to sleep or to nurse with any comfort. For the past two days, its temperature has ranged from 101° to 102° F., the respirations have been very rapid, and the child has had a dusky pallor constantly. As we examine the baby, you will notice that the chest is like that seen in the barrel-shaped emphysematous chest of an asthmatic individual, and on close inspection, you can see that there is, in fact, an expiratory dyspnea. On percussion, the sounds are those of hyperresonance and on auscultation, there are in addition to innumerable moist râles in every portion of the lungs, many sonorous musical and piping râles. The roentgenogram shows diffuse mottling throughout both lungs.

I am not willing to say whether or not this infant has bronchopneumonia. I am sure, however, that he has a capillary bronchitis or bronchiolitis, whichever term you may prefer to use; only a postmortem examination can determine whether bronchopneumonia is also present.

When young infants are infected with the influenza bacillus, the inflammation travels rapidly along the upper respiratory tract, involving the trachea, bronchi, and then the bronchioles in which the small lumen is soon almost, or entirely closed by the inflammatory swelling and exudate. Thus, some air gets into the terminal alveoli, but very little can escape and hyperinflation or emphysema results. This explains the asthmatic type of breathing, the hyperresonance, and expiratory dyspnea. The prognosis in these cases is poor, and in every epidemic of influenza, we see not a few young infants affected with this condition, and many of them die. If death occurs early, there may be found at autopsy a diffuse bronchiolitis, but no pneumonia; but in some, especially if death is delayed a little longer, there will be areas of pneumonia as well.

I have attempted with these 5 cases to present a few of the types of pneumonia seen in infancy and childhood, and to point out the main peculiarities of the child's clinical behavior with some remarks about diagnosis which I hope will be helpful.

CLINIC OF DR. JOHN S. COULTER

ILLINOIS CENTRAL HOSPITAL

MEDICAL DIATHERMY IN PNEUMONIA

THE therapeutic application of high frequency currents to the body produces heat in the underlying structures, and when the heat is maintained within physiologic limits, it is known as medical diathermy. There are two methods of application: the older method is known as conventional or long-wave diathermy, while the newer methods are grouped as short-wave diathermy. It is believed that short-wave medical diathermy is more efficient in producing deep heat in the human body than any other method in use at present.

In our clinic we have made approximately 300 tests of tissue heating by short-wave diathermy machine.¹ In these tests temperature rises in the human thigh were measured by thermocouples inserted 2 inches directly into the quadriceps extensor muscles. The currents were applied for twenty minutes and the temperatures were taken before and after this period with a potentiometer. In a comparison with other methods it was shown that at this depth in the quadriceps muscle short-wave medical diathermy gave an average rise of 4.75° F., conventional diathermy 2.5° F., and hot-water bottles 0.25° F.²

The technical application of short-wave diathermy is less complicated than the conventional contact metal electrode diathermy. This makes its application more suitable in pneumonia.

Short-wave diathermy may be administered by two methods: electromagnetic induction or by the electric field method. In our clinic we have found the electromagnetic induction technic to be the most effective and convenient method of producing heat in the depths of living human tissue. In this method the

current is conducted to the patient from the short-wave machine by means of a flexible heavily insulated cable or a disk electrode containing the cable coiled and positioned ready for treatment.

The electric field method for short-wave diathermy is used by many different technics. The technics accepted by the Council on Physical Therapy of the American Medical Association for this method are the double cuff technic and the air-spaced electrodes so applied that both electrodes are on the same surface of the part to be treated. The double cuff technic is not suitable to treat pneumonia.

The ability to heat the deep tissues with air-spaced electrodes appears to be dependent upon the size of the electrodes, the energy available from the apparatus, the method of application, the distance of the electrodes from the skin and the patient's tolerance.

In our clinical and physiologic research with short-wave medical diathermy, we found no proof that this current has a special selective thermal action, special bactericidal or special biologic action. We believe that the therapeutic results of medical diathermy can be attributed to the effects of heat.

Special Selective Thermal Action.—Coulter and Carter³ made an investigation of heating living human tissues by short-wave diathermy machines of different wave lengths. Their study was made to determine the heating efficacy of short-wave diathermy in living human fat and muscle of the thigh, employing, first, an electric field of 6-, 12-, 18- and 24-meter wave lengths, using the cuff electrode technic; secondly, an electromagnetic field of 12-, 18- and 24-meter wave lengths, using the coil technic. The cuff electrode of the electric field and the coil of the electromagnetic field were selected because previous work by Mortimer and Osborne showed these methods of application to be the most effective of those in general use for heating tissues. The machine used in these tests was so designed that the oscillator circuit could be interchanged, thus giving the range of wave lengths aforementioned.

It was not possible to discover any particular reason why one should select any one specific wave length. Coulter and Osborne⁴ made a study of tissue heating using 6-, 12-, 15-, 18- and 24-meter wave lengths and again they found no significant

difference. They used not only the electric field method, the coil technic of the electromagnetic field but also made a study of the so-called glass "air-spaced electrodes."

Specific Bactericidal Action.—Mortimer and Osborne⁵ in our clinic in their experiments subjected both cultures of staphylococci, streptococci, *Bacillus melitensis*, gonococci, meningococci, and *B. typhosus* to a 6-meter wave for twenty minutes, during which time the temperature of the culture rose to 40° C. without observing any change in the growth of the micro-organisms. They subjected rats with experimental pneumonia for three minutes daily to the 6-meter wave without observing any change in the fatal course.

The experimental work that claims specific bactericidal action for these high frequency currents may be more rationally explained, according to Mortimer and Osborne, on the basis of "point heating," which raises the temperature of the micro-organisms above their thermal death point without a corresponding elevation in the temperature of the medium. It still remains to be demonstrated whether such test tube results can be secured with infection in the body.

Specific Biologic Action.—Mortimer and Osborne,⁵ in reviewing the literature, believe that there is no conclusive evidence from the literature nor were they able to substantiate in their investigations the claim of specific biologic action of high frequency currents (short-wave diathermy). In their opinion the burden of proof still lies on those who claim any biologic action of these currents other than heat production.

Curtis, Dickens and Evans,⁶ in a recent article summarizing their investigations on specificity, state:

"If such an effect exists, it should be possible for the discoverers to describe at least one clear-cut experiment which could be repeated by other workers. In the absence of such evidence we consider that the great mass of inconclusive observations which has been presented is a very insecure foundation for the rapidly growing belief in specific short-wave therapy. Whilst the possible existence of specific actions of ultra short waves cannot be denied, in our opinion such effects have not as yet been adequately demonstrated. We, therefore, find ourselves in agreement with the conclusions of a recent report to the Council on Physical Therapy of the American Medical

Association by Mortimer and Osborne: 'There is no conclusive evidence from the literature nor were we able to substantiate the claim of specific biologic action of high frequency currents (short-wave diathermy). In our opinion the burden of proof still lies on those who claim any biologic action of these currents other than heat.' "

The experimental work on the use of diathermy in pneumonia still rests on the work of Binger⁷ and Christie. They used conventional diathermy and during the passage of the diathermy current they made direct measurements of the temperature which developed within the lungs in normal dogs and in those which were the seat of a pneumonic consolidation. It was found that in normal lungs in no instance was it possible to demonstrate any considerable amount of local heating. The explanation is that the lungs represent an excellent water-cooled system and the intact pulmonary circulation prevents any considerable degree of local heating. In the consolidated lung of dogs, probably because of the disturbed circulation, it was possible to increase the local heating slightly. In 3 pneumonia patients direct measurements of the lung temperatures were made by thermocouples enclosed in an ordinary Luer needle, which were inserted directly into the consolidated lung. In none of these patients was there an appreciable rise in lung temperature during or after exposure to the diathermy current. Cole⁸ says that in the light of these studies carried out in his clinic, he has made no further clinical use of this method, but he hesitates to state categorically that this method has no value.

Stewart,⁹ who has used diathermy in the treatment of pneumonia for fifteen years, believes that there has been a great deal of misconception and misinterpretation of the findings of Binger and Christie. He discusses their results in this article but most of Stewart's objections to the findings were answered by Binger.⁷ In this article Stewart gives 2 series of cases. In the first there were 95 treated cases with a mortality of 12.4 per cent and 59 untreated cases with a mortality of 20.3 per cent. In the second series there were 36 treated cases with a mortality of 19.4 per cent and 21 untreated cases with a mortality of 42.9 per cent. Stewart states that the mortality is reduced at an average of about 70 per cent.

In the last fifteen years numerous articles have been pub-

lished on the use of diathermy in pneumonia. The results have been judged on the statistical method, but usually without a full analysis of all the factors. Karsner and Goldblatt¹⁰ in their article on the "Evaluation of Methods used in Physical Therapy" state that since the statistical method does permit of opinion on the part of the observers, the number of observations must be multiplied so as to decrease this particular factor of error. Further, they state that this error can be practically eliminated by objective evaluation of the effects without knowledge of the type of treatment used. Thus, one experimenter gives the treatment and another makes observations on the patients without knowledge as to which have and which have not been treated. This method does not seem to have been followed in any of the reports on the use of diathermy in pneumonia. Further, the cases treated and the controls were not analyzed for the many factors that enter into the pneumonia picture, such as age, amount of lung involved, heart condition, etc. Several reports have given the types of organism that caused the pneumonia in the treated and untreated cases.

At the Illinois Central Hospital in Chicago we have used for some years both conventional and short-wave diathermy on early cases of pneumonia. Dr. LeRoy H. Sloan, Medical Director of this hospital and Professor of Medicine, University of Illinois College of Medicine, was in charge of these cases. From our study of the temperature, pulse and respiration charts and leukocyte counts, there was no evidence of a specific response to medical diathermy. We have observed that in the management of pneumonia, medical diathermy does seem to be of definite benefit in reducing the severity of the thoracic pain.

This symptomatic relief is often important. The main factors concerned in the production of anoxemia are the passage of blood through the unaerated portion of the lung and shallow breathing. The shallow breathing may be due to pleuritic pain restricting the respiratory excursions. The relief of this pain by diathermy increases the respiratory excursions and this may be the explanation for the decrease in cyanosis that is usually noted.

Sloan believes from our cases that there is a suggestion in the early cases that medical diathermy may have an effect on the pneumonic process. Bazett¹¹ notes that the activity of

leukocytes in phagocytosis is probably greatly modified by temperature. The locomotion of leukocytes *in vitro* is certainly so affected. The maximal velocity is reached at 104° F. Clarke in his study of the activity of leukocytes in the blood vessels of a rabbit's ear in a transparent chamber made a motion picture for the Council on Physical Therapy. This picture shows that under heat the circulation is greatly increased, there is a local increase in the leukocytes and a sticking of the leukocytes to the vessel walls. These facts offer suggestions as to the possibility of an influence of medical diathermy on an early pneumonic process by its stimulating effect upon the body's natural defenses against the organism.

Therefore, it is believed that diathermy is not a specific cure for pneumonia; that we have not accumulated sufficient critical evidence that it lowers the mortality; that while there is a suggestion of its value, we have no evidence to prove its effect upon the course of the pneumonia. It is a helpful adjunct in treatment of pneumonia because it is the best method for the application of deep heat.

In our clinic we use a short-wave diathermy machine that has been accepted by the Council on Physical Therapy as giving efficient heat by electromagnetic induction. The current is conducted to the patient through a flexible, heavily insulated cable formed in a pancake coil of 3 turns with sufficient bath toweling interposed between the cable and the skin. This coil or a disk electrode containing the cable coiled is applied to the chest wall over the pneumonia area.

Heating produced by electromagnetic induction is not necessarily confined to the body of the patient for it is produced in any material or substance in direct proportion to the conductivity thereof. Close proximity, therefore, of any metallic or other conductive articles should be avoided when treatment is in progress so that the patient may receive the full effect. It is also usually necessary to provide a good ground for these machines. The manufacturers of the particular apparatus used will designate whether a ground is necessary or not. A good ground can usually be secured by connecting the ground wire under the metal screw holding the metal wall plate in place, or by connecting the ground wire to a cold water pipe by means of a metal clip. Mattresses with inner springs should

never be used as sufficient heat under certain conditions may be generated in the springs to ignite the mattress material. An iron bed can be used provided the coil is kept at least 1 foot away from any portion of the iron framework. The section of the cable between the plug in terminals of the machine should be separated at least 4 inches. This is necessary because the capacity between these leads, if brought close together, will serve as a shunt for the very high frequency current and will by-pass the part being treated, thus reducing the efficiency of the current. Energy thus shunted will unduly heat the insulation of the cable. For a similar reason it is not advisable to treat a patient resting on an object which is grounded. If this is done, current will be passed into the patient by conduction through the capacitative coupling between his body and the cable. Failure of the circuit to oscillate may result from "too close coupling" between the electrode cable and the patient. This may happen when the electrode cable is positioned too close to the patient or when there are too many turns or loops in it for a given distance between cable and patient.

At Illinois Central Hospital we give at least 2 treatments a day over the involved area. The amount of current is regulated by the patient's skin tolerance. The meter on the high frequency apparatus does not measure the electrical energy passing through the patient. The patient's tolerance is the most important guide for the final dosage to be used. If it is suspected that the heat sensation of the skin over which the electrodes are placed is subnormal, it is advisable to test the skin with hot water in a test tube. In pneumonia the current should be below the skin tolerance. The time of treatment is from twenty to sixty minutes.

SUMMARY

1. In our opinion there is no evidence of a specific response to medical diathermy used in the treatment of pneumonia.
2. In the management of pneumonia, medical diathermy does seem to be of definite benefit in reducing the severity of the thoracic pain.
3. This fact makes it a valuable adjunct in the treatment of pneumonia.

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TREATMENT OF EMPYEMA

ANY symposium on pneumonia would be incomplete without a discussion of one of its frequent complications; namely, empyema. Too often it manifests itself as an anticlimax, just at a time when the hopes of recovery have been warranted. Or, on the other hand, its signs may merge into those of the primary illness and thus make its detection even more difficult. The value of serum in suitable cases and of oxygen therapy in others appears to be established but it appears that the incidence of a complicating empyema unfortunately has not been reduced by these measures.

Ordinarily it does not come within the province of the surgeon to treat pneumonia though he may see it as a post-operative complication or following cases of trauma. Because empyema is a complication rather than a primary disease he does not often observe its development. Though the diagnosis therefore may fall to the one who has been responsible for the care during the pneumonia, it is well to emphasize certain features which are found in proved cases of empyema before drainage. One may become suspicious of the development of an empyema when the fever having subsided rises again. This is more often true in the pneumococcic type forming more slowly and giving evidence of its presence when the signs of the pneumonic process are subsiding. In the streptococcic form it forms simultaneously with the process within the lung. In infants the pneumococcic type may be synpneumonic. During an epidemic of influenza the streptococcic type may predominate though ordinarily the pneumococcic type is more common. In the patient with a large accumulation of pus the physical signs of flatness and absent breath sounds may be sufficient, coupled with the clinical course, to suspect an empyema. A smaller pocket, however, may escape detection because of a minimum of findings. The presence of breath

sounds in children and some adults, over fairly large pockets can easily be misleading. A searching examination may go unrewarded when the accumulation of pus lies along the mediastinum or arises in an interlobar space. An x-ray plate may be the only way of detecting such a collection. However, although an x-ray plate is not necessary for the establishment of a diagnosis in many instances, nevertheless, when such a plate can be secured without too much effort on the part of the patient it should not be omitted. Its greatest value lies in having a record for comparison after drainage to note the progress in the obliteration of the cavity. If for any reason the patient's response to drainage is not what is expected a new x-ray film may show the cause. Two or more distinct pockets are sometimes seen as well as an occasional bilateral involvement. For these reasons the x-ray where available may be invaluable.

The absolute diagnosis is made by the aspiration of pus with a needle. This in most instances is readily accomplished. Sometimes, however, particularly in relatively small collections several attempts may be necessary for localization. One should always introduce a needle of moderate caliber at first and be conscious of the fact that injury to the lung can occur. Where several aspirations are carried out at varying intervals or successive days one may be disappointed at not obtaining pus though the same site is chosen. This is more likely to occur where the original aspiration was near the periphery of the pocket so that now with its reduction in size the lung may have reexpanded and become adherent to the chest wall at that site. On the other hand, anyone with experience knows that sometimes no pus is obtained and the explanation is not obvious because an operation reveals pus and one is at a loss to explain why the needle did not reveal it when a reasonably large pocket exists. An examination of purulent material removed should be made routinely. A smear may be sufficient to show chains of streptococci or pneumococci. Cultures likewise can be taken and aerobic and anaerobic media should be used. Anaerobic organisms frequently render the pus foul. A sterile culture should lead one to suspect a tuberculous basis for the empyema.

Certain physiologic considerations must be constantly borne

in mind in the treatment of empyema. It has been shown that the mediastinum cannot be regarded as a fixed structure, this being particularly true in infants and children. If this be true an open pneumothorax may embarrass respiration by a shift of the mediastinal structures and encroachment on the capacity of the good lung. This will occur where no adhesions exist between the lung and the chest wall. In pneumococcic infections there is laid down considerable fibrin, the development of the empyema is relatively slow and the pus is thick, all tending to favor adhesions between the parietal and visceral pleura. In the streptococcic infection the opposite is true, the empyema occurs simultaneously with the pneumonia, it develops more rapidly, and there is little fibrin early and the pus is seropurulent. It is in this type that an open pneumothorax may allow the lung to collapse, a shift of the mediastinum may occur and with the toxemia of the pneumonia still present cause too great a load on the respiratory and circulatory mechanisms. This danger is obviated of course if sufficient time is allowed for the pus to become thick, at which time adhesions are usually present, or by the avoidance of an open pneumothorax.

There are two objectives in the treatment of an empyema. The first is the establishment of adequate drainage, the other is the obliteration of the cavity. If these are successfully accomplished chronicity and recurrence will be avoided.

Adequate drainage is usually accomplished by the open or closed method. Equally good results are obtained by each method provided that the fundamental principles in the treatment of empyema are observed. Of these principles perhaps the most important one is to avoid an open pneumothorax in an early case of streptococcic empyema or in a very sick patient of any age. A useful procedure in any desperately ill patient is the simple aspiration of some of the pus as the initial procedure. Definite improvement often follows making the drainage operation safer when it is carried out. Occasionally in small pockets aspiration may suffice to bring about a good result making drainage unnecessary. However, to use aspiration as a method to establish adequate drainage will lead to many disappointments. If closed drainage is employed slight suction by any available means may exert a favorable influence toward obliteration of the cavity by the expansion of the lung. Too

great a suction may cause the lung to fall against the tube and pockets to form which can give a great deal of trouble. Irrigation of the cavity with saline or chlorine solution helps to control the infection and wash out the fibrin, thus giving greater expansibility to the lung and hastening the obliteration of the cavity. Small bronchial fistulae usually close spontaneously. Where large ones are present the patient usually raises much of the pleural contents through the bronchial tree. This type is probably better treated by open drainage. The fistula can then be watched and treated if it persists.

When open drainage is used it must only be done after adhesions of the parietal and visceral pleura exists. The resection of a small piece of one or two ribs will always provide adequate drainage. The failures in this method are not due to the method but to failure to maintain adequate drainage. The wound will soon fall together unless attempt is made to keep it open until the lung expands and thereby obliterates the cavity.

Case I.—This x-ray (Fig. 10) is that of a baby three years of age. The haziness at the left base shows some aeration of the lung field immediately above the diaphragm. The suspected area is not very dense. This child had a lobar pneumonia on the left side. The fever had not subsided at any time except for the slight daily fluctuations. The two days before I first saw her, there was a slight cyanosis present, a troublesome cough and constant fever. The child had been ill for two weeks. Aspiration of pus over the dull area posteriorly revealed pus and 60 cc. were removed. Examination of the pus revealed pneumococci and this case illustrates how the empyema developed without any cessation in the febrile course as usually seen in pneumococcal empyema in adults. The following day only a small amount of pus could be obtained by use of the needle and there was no improvement in the condition of the patient except slightly less cough. Closed drainage was then instituted by introducing a catheter through a trocar and irrigations with Dakin's solution was carried out every two hours. The cavity which held more than 150 cc. at the time drainage was established reduced in size rapidly and in two weeks no more solution would enter the tube. The reduction was gradual and the two objectives were accomplished, adequate drainage maintained and obliteration of the cavity. It is a gratifying result in a small child by means of closed drainage which did not require any further surgery because no residual cavity remained unobliterated.

Case II.—This lady is fifty-five years of age. She had a cold which later became severe enough to cause her to go to bed. High fever followed up to 104° F. She was cared for at home where adequate nursing care and an oxygen tent were employed. At the end of ten days she appeared to be better

for several days when her toxemia which had not at any time subsided was increased. She was irrational at times and took very little nourishment by mouth. There was evidence that the consolidation in the right lower lobe was undergoing resolution. No new involvement could be detected on physical examination. She was then moved to a hospital where an x-ray film (Fig. 11) revealed a large circumscribed density on the right side in midfield. The upper lung field was clear as was the costophrenic angle and adjacent area. Localization of this collection by x-ray allowed for even more careful examination of the chest but the findings were similar. Breath sounds were slightly suppressed but present throughout the right side, and no dullness could be elicited. By the absence of peripheral signs with the positive x-ray findings in the location of the interlobar fissure, an interlobar empyema is suggested.



Fig. 10.



Fig. 11.

This condition is really an abscess and is best treated as such. Aspiration with a needle may reveal pus but this procedure is not without danger because if no adhesions exist a free pleural space may be infected which usually proves a very serious complication in an already very toxic patient. An open operation is therefore indicated in this condition. If a point of tenderness can be found on the chest wall it is strong presumptive evidence of involvement of the pleura at that point and the collection lies most superficial at this point. A mid-axillary incision is usually suited for exploration with a needle in any direction provided the adhesions are found to be present. This was done in this patient, pus aspirated and drainage established. Tubes were inserted to facilitate drainage the cavity quickly reduced in size with the evacuation of the pus, the fever subsided gradually in a week. The tubes were gradually shortened as the cavity obliterated itself.

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THE USE OF OXYGEN IN PNEUMONIA

PNEUMONIA is a killer. All pneumonia cases are emergencies and require care from the time the diagnosis is made until the patient has recovered. It is doubly dangerous because a prognosis can scarcely be stated. One well-known internist was heard to say: "I never express a prognosis in pneumonia for over twenty-four hours at a time and dislike to do even that." An apparently "mild" case may take a "turn for the worse" and in a few hours be moribund. Treatment in pneumonia (with the exception of specific serum treatment) is supportive; that is, the patient is to be kept alive by any manner of methods which will accomplish this purpose. He must be supplied with fluids and with food. And in addition he must be supplied with oxygen when his lungs are out of commission. Probably it is more important that he be well "fed and watered," but oxygen comes so near to equal importance with the proper supply of water and carbohydrates as to be of equivalent value.

Mode of Death in Pneumonia.—Certain pneumonias terminate because of septic complications. This number includes the endocarditis cases. Such an end is rare. Some more end in empyema. The great majority terminate in circulatory failure, whether they be bronchopneumonia or lobar pneumonia.

A typical termination is illustrated by the following case:

Case I.—A man, forty-eight years old, had a cold for two weeks with running nose and slight cough but had continued his printing work. At 6 p. m. on February 12th he had a "few chills" lasting about thirty minutes and then became very hot, perspiring freely. He became so weak he could scarcely move. There were many pains in the joints and the back. About midnight he

began to cough and to raise a bright red sputum. The cough caused some chest pain on each side.

On entrance to the hospital on February 13th, the notation reads "man about 45 lying in bed, ill but apparently not seriously so. Temperature 102° F., pulse 104, respirations 24, blood pressure 150/70." There were physical findings of consolidation over the left lower lobe. *No cyanosis* was present. On February 14th the progress note includes: "Patient appears more comfortable today." The chest findings were unchanged. However, that afternoon the temperature reached 104° F., the pulse 130, while the respirations still remained about 25 per minute. He was resting quietly on small doses of codeine and taking food and fluid well by mouth.

On February 15th his temperature reached 103° F., pulse 120 and respirations 30. Between 6 and 9 p. m. a rapid change developed. The slight cyanosis first seen in the afternoon of the previous day deepened sharply. The respirations were 44, pulse 140, and the temperature 102° F. The skin felt cool. The patient was irrational but quiet, would take little fluid by mouth, and kept complaining of pain in the left side. He seemed a bit more comfortable propped up in bed. He raised a large quantity of foamy red sputum which could also be heard as tracheal râles at his bedside. He was obviously very ill. The blood pressure was below 100 systolic. Fluids were given into the vein.

On February 16th his blood pressure in the morning was 154/64. He again seemed fairly well stabilized, although his axillary temperature was 102.6° F. and pulse 120. His breathing was uneven. He could not pass water and, hence, was catheterized. He was moderately distended. However, he seemed somewhat brighter and was rational. By late forenoon the sudden change of the day before had begun again. The pulse continually rose, 136 at 11 o'clock, 140 at 3 o'clock, 148 and irregular at 6 o'clock. Cyanosis had deepened. The cough reflex was lost, tracheal râles were loud, and he died with a temperature of 102° F. axillary at 6.15 p. m. The skin was wet and warm but not hot the last two hours.

This record includes the following facts: a man definitely but not desperately ill died in three days' time. Each turn for the worse appeared rather suddenly within a few hours, and was especially featured by a rising pulse rate. There was no engorgement of the veins. Cyanosis progressively developed and deepened. Terminal changes were rapid.

We can read into the record an increasing oxygen want, increasing need of food and fluid, increasing distention, an absence of progress or extension of the pneumonia, and a rather sudden death in circulatory collapse resembling *shock* but not resembling the congestive heart failure seen when the heart gives out.

At necropsy the usual thing is to find the lungs partly consolidated, the nonconsolidated parts being heavy and edem-

atous. The heart is usually firm, still perhaps in rigor mortis. The myocardium has a fairly good color and is not friable. Most interesting is the engorged liver and the congestion of the entire splanchnic area. Even in death the great veins are collapsed. There is no postmortem evidence that the heart muscle has played out. Of course, certain cases do end in congestive heart failure, decompensation, but for the most part these are people with previously damaged hearts, *i. e.*, an old rheumatic myocarditis with mitral stenosis and fibrillation may well decompensate during a pneumonia and, outliving his infection, die a bit later from congestive heart failure.

Nature of the Circulatory Failure.—It is increasingly evident that the sudden bad change in a sick pneumonia patient is the appearance of increasing pulse rate, graying of the cyanosis, a change of skin temperature, becoming cool and moist and a falling blood pressure. The rectal temperature rises. These are mostly phenomena of shock. The blood pressure may not fall until only a few hours before death. It will fall, however, any time too little blood returns to the heart to be pumped out and maintain a pressure head. Absence of venous engorgement at this stage is significant. The veins are not full; they are empty and collapsed. The finding of hemoconcentration is significant and well confirmed in both pneumonia and shock. The necropsy findings of much blood in the splanchnic region supports the idea that diminishing blood volume permits a progressively smaller venous return and a diminishing cardiac output. The word "exemia"¹ has been used to convey this concept of a shocklike situation arising independent of pain in the presence of severe toxemia.

Rôle of Fluid Loss in Causing Circulatory Failure.—Dehydration is not tolerated by a pneumonia patient. He needs much fluid because of the rapidity with which he loses fluid as sweat and as urine. He must secrete a certain minimal amount of urine, probably about 800 cc. daily, or else retain some nitrogenous waste. It is well known that fluids are a life-saving measure in the presence of any hemoconcentration. This is best seen and studied in shock. Dehydration is important in pneumonia, since it may be the trigger mechanism of inducing peripheral circulatory collapse. It is, of course, better prevented than treated after it has developed fully, for we have

seen that this circulatory failure may be quite rapid once initiated.

Rôle of Toxemia in Causing Circulatory Failure.—The rôle of toxemia in causing circulatory failure is not clear-cut. Presumably the capillaries, especially in the splanchnic beds, respond to a circulating toxin by dilating and becoming more permeable. Blood passes then more slowly through these beds and loses fluid from its plasma at the same time.

Oxygen want is known to injure capillaries and lead to their dilatation and stasis within them and thence to loss of circulating fluid and rise in hemoglobin. It may be that prevention of oxygen want may prevent the terminal chain of events.

Rôle of the Heart in Causing Circulatory Failure.—The rôle of the heart in causing this circulatory failure is probably negligible. It is at fault only in that not enough blood reaches it to be pumped into the arteries and maintain a pressure head in them.

Rôle of position is probably of little importance, but an erect position will not permit endurance of very low blood pressures.

Effect of venesection in these desperately ill, cyanotic patients is best discovered by review of somewhat older literature. In a series of 14 influenzal pneumonias so treated during the epidemic, 13 died in such condition as to demonstrate that the blood loss induced the picture of toxic shock.²

The Action of Oxygen in Preventing Circulatory Failure.—Case II.—Miss B. G., a Scotch girl, thirty-two years old, developed a pain in the left chest on the third day of an afebrile cold. She had had some cough and prostration at first. The pain kept her from rolling over and from coughing. The evening of the third day of her illness her respirations were 30, shallow and grunting; pulse 112 and temperature 100.4° F. Physical findings of consolidation were present over the left lower lobe. At 10.30 P. M. that night at home she was given about 10 cc. of mixed 1 and 2 serum when an anaphylactic reaction developed with sudden collapse, appearance of very extensive urticaria, cyanosis, rapid breathing and stupor. The radial pulse disappeared. Adrenalin and caffeine were used at once and after a few hours she seemed about as before. She was hospitalized next morning, the fourth day of her illness, with a temperature of 100.4° F., pulse 104, respirations 28 and blood pressure 124/76. She was somewhat cyanotic about the lips and hands. She was placed on oxygen by oropharyngeal insufflation at once. The cyanosis faded, the breathing was easier. In spite of careful attention to water balance and feeding, she did not do well. Consolidation appeared in the right lower

lobe and numerous râles were present throughout the upper lobes. Often her respirations were above 40 and the pulse above 120. The blood pressure was sustained above 110 systolic and 80 diastolic. Streptococci were found in great numbers in her bloody sputum and shown by culture to be hemolytic.

On the third hospital day, while cyanotic despite efficiently administered oxygen, the tank became empty and some delay arose in changing it. Inside of seven minutes she was intensely cyanotic, orthopneic, the skin became cool and wet and the pulse rose to 160. The intern's note includes this sentence: "In this brief time she came very close to death." Within a few minutes after oxygen was started, the tachycardia was less than 140 and breathing again about 40 per minute. On two other occasions the same thing happened but in shorter periods. Eventually she recovered after getting oxygen continuously for twenty days. Her arterial blood while getting oxygen was 77 per cent saturated with oxygen, and while without oxygen was 54 per cent saturated; 77 per cent saturation corresponds to an altitude of about 25,000 feet.

The acute collapse symptoms seen upon withdrawal of oxygen can be considered as "held back by its administration."

Causes of Oxygen Want in Pneumonia.—In the July issue of the magazine *Fortune*, there appeared a concise, well-written article entitled "Oxygen." It was about the possible effects on aviators of oxygen want at altitudes of 10,000 feet and more. The point to this particular write-up was that oxygen want might lead to certain "pilot errors." The physiologic writing was suited to lay readers and probably some of your patients have already read it. At increasing altitudes the air contains the same percentage of oxygen as at sea level but the barometric pressure falls so that the normal human hemoglobin exposed to such an atmosphere will not be 95 per cent saturated, as is the case at sea level pressure, but less than that. It is well known that pneumonia runs a peculiar and severe course at heights of 3000 feet or so.

In pneumonia, oxygen want arises because: (1) shallow breathing does not properly ventilate the lung; (2) some blood circulates through a consolidated and airless lung; (3) edema fluid prevents the ready diffusion of oxygen from the alveoli into the pulmonary capillaries.

Breathing in Pneumonia.—We all remember the breathing in cases of pneumonia. An adult breathing more than thirty times a minute rarely fails to attract attention. In pneumonia the breathing is usually such an effort that the patient seems to be laboring. The breath may be checked after a partial inspiration as though the pain halted complete inspira-

tion, and then the expiration comes with a grunt. The nostrils flare with each breath. In a typical case the respirations rise each day, becoming 40 or more. When the breathing is this fast, can it be effective in getting air into the blood in the capillaries of the lungs? It certainly is too shallow to permit the patient to speak easily. Speech is broken and difficult. When a man breathes so fast from pneumonia, he takes in and out with each breath much less air than a normal subject. This volume of air breathed each time is called the tidal air. In health, at rest, this tidal air is, say, 500 cc. This would be adequate to get a fresh supply of oxygen through the dead space of trachea and bronchi into the alveolar spaces. About 150 cc. can be used as an approximation of the dead space. When shallow breathing comes, it can be borne for a time, if not too shallow. But when the tidal air gets to 200 cc. or less, little goes *past the dead space into the alveolar spaces which contain the residual air*. The residual air in health is roughly the 1000 cc. of air which we cannot voluntarily blow out of our lungs, even with a forced expiration. This residual air is confused at times by students with the vital capacity. The vital capacity is simply the greatest volume of air a subject can expire after taking a big breath. This measure differs widely in different subjects and ranges from around 5 liters in a big man to perhaps 3 liters in a healthy but small woman. In pneumonia, however, it is greatly reduced for the patient can neither take a big breath nor expire fully. All the sick man can do is hope to get another breath each time. Pneumonia patients are conscious of their difficulty in breathing! There is something akin to agony in the struggle for breath. Most of us find this need of air, or air hunger, very distressing. Perhaps it is as bad as pain. It must be a cause of anxiety and fear and the effort to breathe is a part of the exhaustion in pneumonia.

The faulty respiration then is fixed rather closely by sharp limits to expiration and to inspiration. The patient cannot breathe deeply but must get along with a little more air at each breath than his dead space.

You have seen children breathe this way as shallow and fast as adults do. But the children do not mind it so much. The difference in adults and children lies in how much of the tidal air really gets into the residual air, down in the alveoli.

The dead space in children is quite small in relation to that of an adult. A child of five might well have a dead space in the bronchi, trachea, pharynx, nose and mouth of 30 cc. or so. Hence, a ventilation of 60 cc. per breath gets 30 cc. of fresh air into lungs, of which the air content at the moment might be 300 cc. In an adult the same effective ventilation would result by getting 90 cc. per breath into lungs having a volume of 900 cc. To get 90 cc. over and above the dead space requires about 230 cc. per breath. Many pneumonias in adults prevent breathing this deeply.

Oxygen administration aims at enriching the atmosphere breathed by the sick man so that all the air which gets past the dead space initially is composed of 40 per cent oxygen (or higher). This may permit shallow breathing to still maintain a high oxygen content in the alveoli so that all blood that passes an air-filled alveolus gets saturated with oxygen.

The amount of blood which passes through airless lung must be relatively small. During the stage of gray hepatization and resolution it seems at a standstill, except for that blood coming through the bronchial arteries. Injection studies of postmortem material illustrates the difficulty of getting anything into the consolidated zones. In bronchopneumonia there is usually circulation through part of each consolidated nodule. Since certain pneumonia cases are seen which persist in having normal oxygen content of the arterial blood, these prove that the circulation is all shunted through the aerated lungs.

The importance of moisture presenting an impedance to the passage of oxygen from alveoli to capillaries cannot be determined by measurement, but must be of marked degree.

Symptoms of Oxygen Want in Pneumonia.—All tissues suffer when deprived of an abundant oxygen supply. The brain especially is affected, depending upon the severity of the oxygen lack and the rapidity of onset. In acute experiments with normal subjects anoxemia resembles drunkenness. The little game of the Eskimo boys (described by Freuchen³), wherein they are hung up by the hood of their furs until cyanotic and then stuporous, illustrates a crude way of getting intoxicated. In these games the oxygen lack appeared in only a few minutes.

In most pneumonias oxygen lack develops progressively over several hours or a few days. This insidious but rapid

change leads to the following nervous symptoms: irritability, restlessness, uneasiness and apprehension, loss of finer motor control, impairment of memory and judgment, diminution of vision and slight headache. This progresses to stupor and to coma, finally reaching the fourth stage of anesthesia—complete asphyxia. Delirium may come from this alone at any time. Air hunger and anxiety are almost constant. Yawning, sighing and irregular breathing suggest oxygen want.

Cyanosis is a bluish coloration of skin and mucous surfaces seen when the blood in the capillaries and venules is largely in the reduced state. In 1923 Lundsgaard and Van Slyke⁴ were co-authors of a monograph on cyanosis. The details of the production of this finding were thoroughly reviewed and checked. These authors demonstrated that about 40 per cent of the blood in these cutaneous vessels must be present as reduced hemoglobin before a bluish cast can be seen. Normal venous blood is about 65 per cent saturated with oxygen so that only a slight further reduction than is normal should lead to cyanosis. Hence, this should be a sensitive index to oxygen want.

There are certain objections to this reasoning. First, anemic subjects can get severe anoxemia and still show no cyanosis. Even if all their hemoglobin were reduced, there still might be too little to lead to cyanosis. A second difficulty is that of getting two observers to agree on color changes of minute degree. A third objection is that skin coloring may make its recognition difficult. A fourth is that there is a variation from one time to another in the same patient.

Therefore, a logical conclusion is as follows: cyanosis undoubtedly indicates oxygen want, *but oxygen want, especially if not too severe, may occur without cyanosis.*

Recognition of Presence of Oxygen Want.—The presence of cyanosis proves oxygen want. But also the presence of nervous symptoms of oxygen deprivation, when seen in the presence of any situation known to be liable to lead to anoxemia, should make the diagnosis of anoxemia clear cut, even without cyanosis being present.

We can recognize actual anoxemia and potential anoxemia. If we were equipped to do arterial blood studies easily and frequently, the laboratory could settle quantitatively the question: "Is this man in oxygen want?" We may come to see that

a routine procedure. At present most people seem to hesitate to do arterial punctures. The arterial blood normally carries 95 per cent of all the oxygen it can absorb when freely exposed to air.

Tachycardia, irregular, uneven, sighing and yawning respirations support the diagnosis of anoxemia.

Difficulty in Compensation for Oxygen Want.—Take a normal athletic man and transport him rapidly to an altitude of, say, 10,000 feet, at which level his arterial blood is approximately 87 per cent saturated with oxygen. He notices he is breathing more deeply than usual, that his pulse is elevated and that his capacity to do work is cut down. He must move slowly. He may become nauseated, dizzy, restless and weak. After a few days his red count rises, *i. e.*, each unit of blood becomes a more efficient carrier of oxygen and he gets used to his environment. At greater altitudes, say 16,000 feet, within several hours he will be bothered with many nervous symptoms. There will be a headache, loss of appetite, restlessness or lethargy, impaired judgment, diminution of special senses, slowed reaction time, even stupor, dizziness, memory loss, and very sharp weakness and fatigue. Later vomiting comes in.⁴ He may still get acclimated.

So mountain sickness acts. It is really oxygen want. But in pneumonia these degrees of oxygen want are the rule. In asking pneumonia patients to endure anoxemia, we are asking that they do something most of us in health cannot do easily. But the pneumonia patients are handicapped. They cannot breathe deeper and faster. Their circulation rate cannot be greatly increased. They cannot rest but must continually *do work* to get rid of the excessive heat produced by their elevated metabolism. No acclimatization is possible for them.

Effective oxygen administration should minimize the oxygen want, quiet the patient, simplify his nursing care, diminish the likelihood of a circulatory collapse. Its value in the control of delirium is exemplified by the following case:

Case III.—R. E., aged sixty-two years, a man well known as a heavy drinker, was ill for three days with chills, fever, prostration, cough and chest pain. He was given a quinine derivative during this time and adequate alcohol. Hospitalization on the fourth day was while the patient was cyanotic. He was fibrillating, having a rate at the heart of 160 per minute. Oxygen was

started on entrance, using the catheter in the oropharynx at a flow of 8 liters per minute. He was irrational but helpless. Unable to take fluids, they were supplied intravenously. His temperature rose during the night to 104.8° F. rectally. His sputum showed pneumococci of a higher type, for which no antiserum is available. He remained in a quiet delirium for forty-eight hours. His appearance was that of a sick typhoid patient. Only for a period of about three hours was his delirium at all likely to lead to exhaustion. The afternoon of his second hospital day he was continuously moving about in bed and talking or muttering. Morpbine, $\frac{1}{6}$ grain, was adequate to quiet him then. It seemed most surprising that he had not developed a delirium tremens. Everyone was expecting such a change. The third day he slept all day long but could be aroused to take fluids. When the oxygen flow was interrupted for a few minutes to change tubes, he again became cyanotic. Only the left lower lobe showed evidences of consolidation at any time. The fourth day his temperature began to fall by lysis. The apical rate was then 112 and respirations only 20. He was mentally clear.

It is my own opinion that chronic alcoholic cases are of all cases the ones most benefited by effective oxygen therapy. The terrors of violent delirium can be controlled with much less sedation, if oxygen is well supplied.

Control of Fever.—Control of fever is commonly ascribed to the correction of anoxemia. We have no record which would prove that, since there are relatively few cases treated only with oxygen. The balance have had some specific therapy as well, so that no conclusion can be drawn as to which procedure accomplished the desired result. A case showing a very favorable course is:

Case IV.—J. McG., a man, thirty-three years old, entered on May 4th. Nine days before he caught a cold with sore throat and went to bed. He was in bed five days, then got up and returned to his work as letter carrier. The evening of his first working day he came home with extreme fatigue and weakness. He was coughing and had a slight chill. Headache was his chief trouble, in fact so bad that it kept him awake all night. The next afternoon at 5.30 P. M. the patient developed a very sharp pain in the right chest and had a full-blown chill. The cough became increasingly painful and he was raising bloody and rust-colored sputum. Deep breathing made the pain worse. He was admitted the following day, the second day after the first chill and twenty-four hours after the onset of acute chest pain.

He was acutely ill, sitting up in bed by choice, the nails and lips cyanotic, the breathing shallow, rapid, with an expiratory grunt. Temperature was 105.4° F., pulse 142, respirations 32, blood pressure 130 90. There were findings of consolidation over the right upper lobe. He did not seem dehydrated. He was confused mentally but cooperative, taking fluids readily by mouth.

The temperature fell, 105.4° F. at 4 P. M., 104.6° F. at 8 P. M., when oxygen was begun, and 101.8° at 10 P. M., when antipneumococcus serum type I was first given. The respirations fell in this time from 40 to 28 and he became quiet. The pulse fell from its peak of 142 to 130. The change during this two hours was most impressive. The patient was no longer restless. He was having much less difficulty in breathing at 1.30 A. M., having had 30,000 units of serum between 10.30 P. M. and 1 A. M.; the temperature was 99° F., pulse 104 and respirations 26.

The Time for Use of Oxygen.—A recent review⁶ states that "It is agreed that oxygen is indicated in pneumonia only when there is cyanosis." In this case I wish to present a minority opinion for which there is much precedent in the legal profession.

There must be a time, in any case which develops cyanosis, that there is a borderline condition in which it may be doubtful whether or not oxygen is needed by the tissues. If the arterial oxygen saturation must fall to 85 per cent before cyanosis is apparent in a given case, there must be some time when the arterial oxygen saturation is about 90 per cent. Now 90 per cent saturation may not lead to cyanosis, yet this corresponds to moving a normal man to a height of 8000 feet (Fig. 12).

Already statements have been made reviewing the effects of oxygen lack. Has there been proof that these harmful influences on the capillaries do not start until cyanosis is present? If a few of us can perform all our work perfectly at 8000 feet altitude, is that evidence that the pneumonia case can equally well endure this "anoxemia without cyanosis?"

Recognition of what has been labeled "potential anoxemia" constitutes an indication for oxygen inhalation therapy. If at all times the oxygen saturation is 92 per cent, then no cyanosis will appear and that patient will shift into the group of pneumonias with a lower mortality.

On such reasoning—that we are unable to appreciate the importance of mild oxygen want situations—I prefer to use oxygen at the onset of a pneumonia, whether cyanosis is present or not. Haldane⁷ writes in his monograph on Respiration: "... for it is now evident that even a very slight degree of continued anoxemia is of much importance to the patient. . . Mountain sickness and carbon monoxide poisoning are not isolated phenomena unrelated to the rest of physiology and path-

ology, but symptoms of anoxemia, which in reality is one of the commonest conditions during illness."

The time to stop oxygen may be a question. Its continued use cannot be harmful (if properly handled), so it seems wisest to continue it until the patient demonstrates that he is no longer toxic and prostrated and that his fever is largely gone. The concentration of oxygen can, of course, be changed from time to time. There is a danger that an anoxemic subject treated

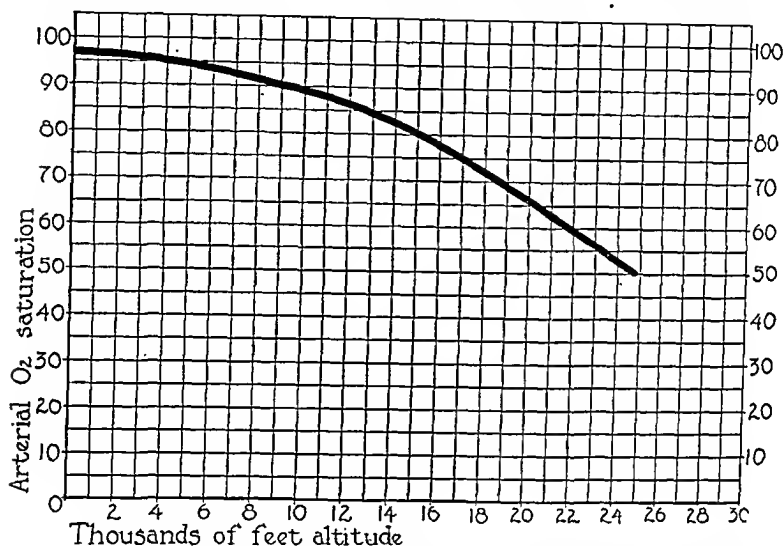


Fig. 12.—This graph illustrates the extent to which a man's arterial blood will be saturated with oxygen at certain altitudes (not fully allowing for acclimatization); 90 per cent saturation corresponds to 9000 feet; 80 per cent to 15,000 feet altitude. Relatively mild anoxemia seen in pneumonia is, therefore, equivalent to a very considerable altitude. (The arterial oxygen saturation on this graph is in percentages.)

with oxygen and then suddenly taken from it may collapse. A good way to prevent this is to withdraw the oxygen for periods of fifteen minutes to one hour, watching for a rise in the pulse rate. If no rise appears, the oxygen is resumed for an hour or so and the trial repeated. If the pulse still remains unchanged and there is no sharp change otherwise in the patient, it can be stopped.

Error is usually made in withdrawing oxygen while the patient is still quite sick, placing again some burden of an-

oxemia—perhaps without cyanosis—on the man who can with most difficulty endure it.

Carbon Dioxide Inhalations in Pneumonia.—Prevention of hypostatic pneumonia in older people confined suddenly because of a broken hip or other injury is usually carried out by moving them frequently, etc. It seems desirable to have such patients breathe deeply so as to prevent the collapse of certain parts of their lungs. Such atelectatic parts are held to be particularly liable to infection. Surgeons now use carbon dioxide inhalations postoperatively to get the patient to breathe deeply and fast, to open up all the lungs. A common procedure is to have a patient breathe carbon dioxide and oxygen from an anesthesia machine and face mask. The gas mixture is usually 5 per cent carbon dioxide and 95 per cent oxygen. Rebreathing should be avoided since the carbon dioxide may build up in a small rebreathing bag pretty rapidly. The inhalations of carbon dioxide can be continued until the patient breathes deeply several times. When I breathe such a mixture, I become conscious of the deep breathing, then feel very tired and have some lassitude, then a headache starts which is a real pain and about then I end the experiment. Please try this on yourself before using it on sick people! There will then be no chance of giving anyone too much carbon dioxide. It is possible to induce convulsions and death by too prolonged carbon dioxide breathing. This can readily happen during poor anesthesia where the soda-lime cannister is not removing the carbon dioxide and rebreathing builds it up.

A safe rule is never to use carbon dioxide continuously! Another is to exercise great caution in its use on any irrational or comatose subject.

Recently two men in California⁸ wrote up the use of such periodic inhalations of carbon dioxide and oxygen as a treatment for all pneumonias. I cannot appreciate any desire for its regular use, but can imagine certain applications, as in older people after fractures, after strokes, accidents or operations, wherein movements are restricted. A case of Dr. Keeton is in point.

Case V.—A woman, fifty-seven years old, told of the onset of pneumonia after a cold. She was particularly dyspneic and cyanotic. Cough bothered her

little. The dyspnea was an exaggeration of earlier trouble for she was quite emphysematous. The physical examination revealed many asthmatic wheezes throughout the lungs but no evidence of consolidation. An x-ray showed questionable pneumonic change in the right lower lobe. She was breathing above 36 and shallowly. Oxygen was given for eight hours with no apparent change. Her marked cyanosis was not affected. The temperature after this trial with oxygen had not changed, remaining 102° F. Five per cent carbon dioxide in 95 per cent oxygen was supplied by an anesthesia apparatus every three hours until she took several deep breaths. Each time this was done she felt better, became free of cyanosis and lost her restlessness. Forty-eight hours later she was temperature-free and apparently out of danger.

Methods of Giving Oxygen.—Effective oxygen therapy can be accomplished in a variety of ways. All of them actually raise the oxygen content of the air within the alveoli. The

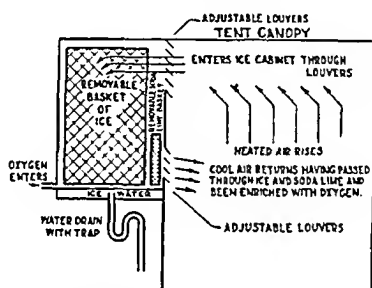


Fig. 13.—This type tent has a good circulation because the air passes over ice and settles while cool (Kotkis and Banash, Hospital Progress, October, 1936).

choice of method depends upon many circumstances. Everyone can easily understand the principles of the effective use of two or three such methods and be able to use whatever plan best fits his immediate needs.

The purpose of any oxygen administration procedure is to raise the oxygen content of the alveolar air. In the use of an oxygen chamber the patient lies in an atmosphere of 40 to 70 per cent oxygen. The method is almost ideal, because it permits a nurse to work easily, the patient is unaware of any special apparatus and such units are always well controlled by analyses of the air in the room. Relatively few chambers are available, though the present method of modifying an ordinary hospital room for this purpose reduces the cost of the installation to \$2000 or less so that others may be arranged.

An oxygen tent is a small portable oxygen chamber built of fabric. The air is circulated through ice, either by convection (Fig. 13) or a blower (Fig. 14) to keep the temperature low enough to be comfortable and to keep the humidity down. The oxygen content of a tent can be kept as high as 70 per cent or above by competent operation. The check on the efficiency of the procedure is the analysis of the air within the tent; this must be done often, preferably every two hours. The analysis is simple and can be done by untrained help, if necessary (Fig. 15). The common faults in the use of tents are as follows: the equipment, because of deterioration of rubber, may leak

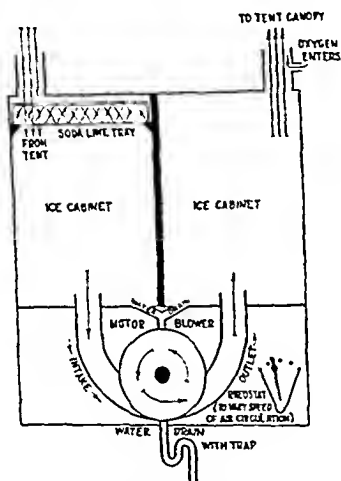


Fig. 14.—This tent has a forced circulation by blower (Kotkis and Banash, Hospital Progress, October, 1936).

badly; the nursing attendants may fail to fold in all the edges and to keep a rubber sheet over the mattress; there is difficulty in getting the patient to take fluids; other nursing procedures may be difficult; breakdown of the motor blower can occur at the worst time; movement of the patient always disturbs the arrangement of the tent walls.

In the hands of personnel skilled in use of tents and with a good nurse in *constant* attendance, the tent becomes a splendidly effective way of administering oxygen. It will require watchfulness by the physician to make sure the patient is comfortable and the oxygen concentration is maintained at the level he ordered, 40, 50, 60 or 70 per cent.

The oropharyngeal insufflation is an effective way of giving oxygen. This method, a modification of the nasal catheter,

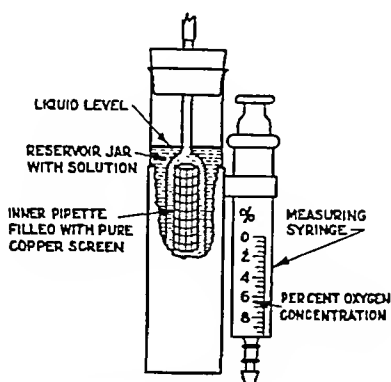


Fig. 15.—This analysis device absorbs oxygen in ammoniacal cuprous chloride. The amount so absorbed can be read on the syringe (Kotkis and Banash, Hospital Progress, October, 1936).

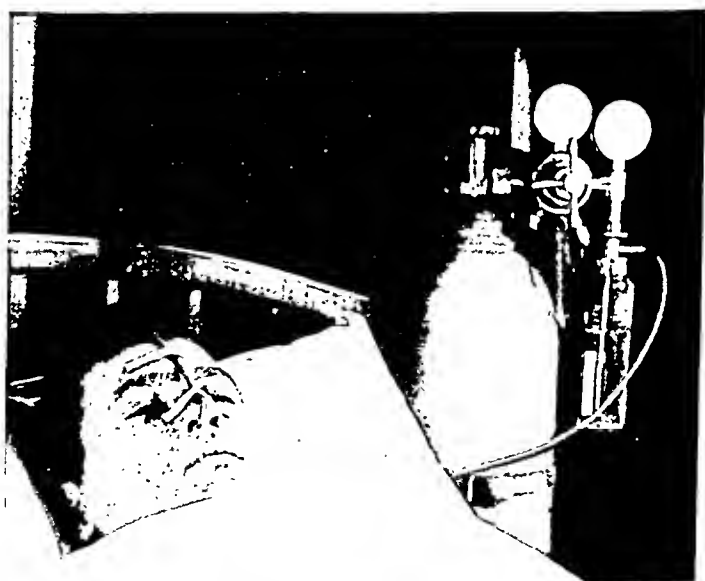


Fig. 16.—Oropharyngeal insufflation in use (Kotkis and Banash, Hospital Progress, October, 1936).

depends for its effectiveness on maintaining an oxygen flow through a tube in the oropharynx.⁹ In this position a stream

of oxygen flows into the oropharynx as far down as possible without making the patient swallow oxygen. Unless the patient is comatose the heavily vaselined tube can be passed through the nostril and into the pharynx until he swallows the gas, then withdrawn just to the point where he stops swallow-

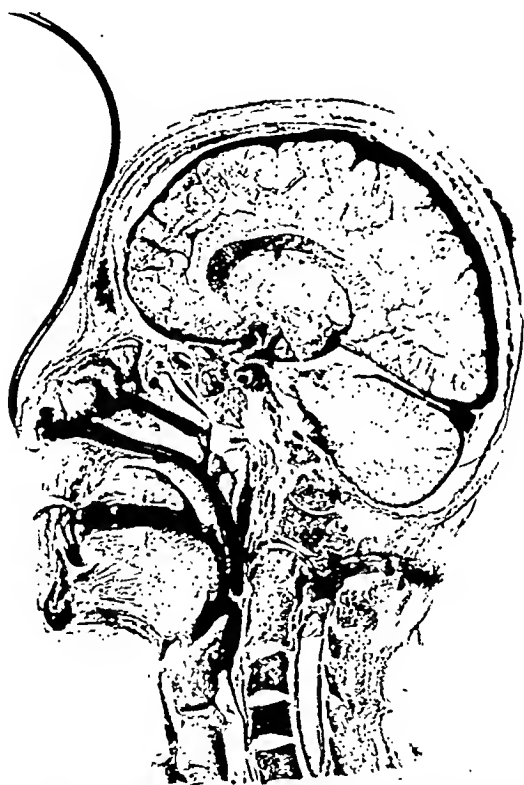


Fig. 17.—Sagittal section of the head showing proper position for the tip of the catheter in the oropharynx (Kotkis and Banash, *Hospital Progress*, October, 1936).

ing. The catheter can then usually be seen in the throat. Then the tube is taped up out of the way (Figs, 16, 17).

The gas should be moistened in order that the stream does no injury by impinging for hours on a given spot in the pharynx. If dry oxygen were so used, an ulcer might result.

The method is simple. requires only a high pressure tank of

oxygen, a reducing valve and a catheter with connecting tubing. The humidifier is advisable if the gas be given for several hours at a time as is, of course, usually true. The humidifier can be purchased. It can be improvised in one of several ways. An easy one is diagrammed (Fig. 18), using milk bottles and passage of the gas through wet gauze. Since glass bottles can always break, it would be best to protect these by netting or towel or by placing them in some container like a wastebasket.

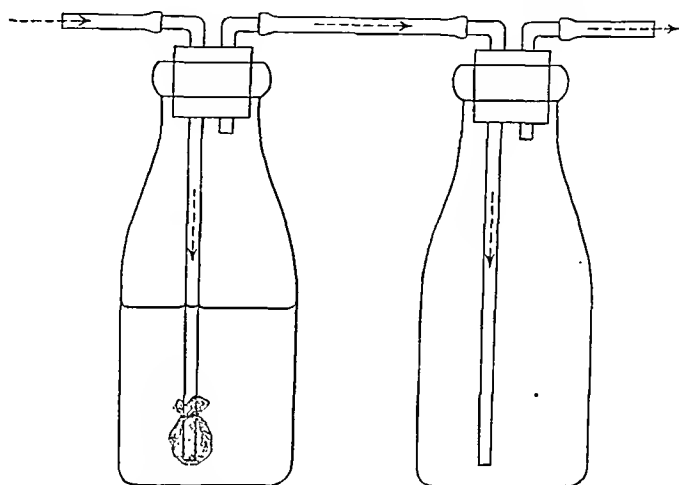


Fig. 18.—A good humidifier can be improvised from 2 milk bottles. Gas bubbles through gauze tied over the end of the inflow tube and the fine bubbles rise through a few inches of water. The second bottle is a trap. Both bottles might well be placed in a waste paper basket or wrapped in a towel.

The common errors in use of the catheter are: (1) inadequate lubrication (must be vaselin on the catheter); (2) infrequent changes (should be at least every twelve hours); (3) improper placing (must not be up in the nose); (4) inadequate moistening of oxygen; (5) inadequate or intermittent flow. Here again continuous nursing care is almost requisite for really satisfactory work. The method does not lend itself to easy check by analysis since there is no simple way to get samples of the man's alveolar air. Such checks on the efficiency of the oropharyngeal method are almost research problems and not to be undertaken lightly.

The Burgess box or inverted tent (Fig. 19) is an ingenious

arrangement by which chilled oxygen is admitted over ice to a box which fits about the patient's head and which has an open top. The cooler oxygen tends to sink and diffuse into the room air at a slow rate so that therapeutic concentration can be reached. This can be tested by any analysis device.

Bullowa's double nasal cannulae (Fig. 20) and Barach's double nasal catheter both work on the principle that a continuous flow into both nostrils is as good as a continuous flow into the oropharynx in that the bilateral administration limits the backflow outward through the nares. Barach's face mask



Fig. 19.—Burgess open type tent (Kotkis and Banash, *Hospital Progress*, October, 1936).

is one of the newest such devices. It does not require moistening the oxygen.

Beyond a certain point cost of oxygen therapy cannot be considered a major part of the cost of pneumonia. The major expenses in most pneumonia cases include private nurses, hospital rooms and loss of time from usual employment. The oxygen is a large item, of course. In point of cost, I am of the opinion that any pneumonia case requiring oxygen requires also constant attendance. I feel that a trained nurse should be beside any tent in operation on such a case. Repeatedly

the oropharyngeal catheter method has functioned satisfactorily in home conditions with attention twice daily by the medical attendant and continual nursing by someone in the family. Repeatedly floor nursing has adequately attended cases so handled. The oropharyngeal method is, therefore, particularly suited for situations requiring low cost. If a large volume of oxygen is so used, many economies can be devised to further reduce the cost of oxygen to the patient per hour. Favorable

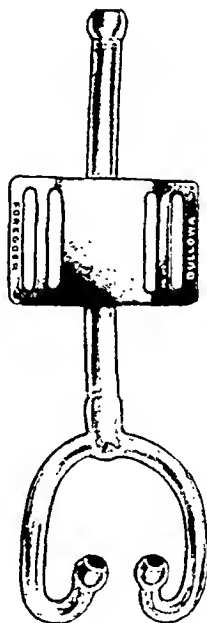


Fig. 20.—The cannula devised by Bullowa straps on the forehead and fits into the nose comfortably.

purchase of U.S.P. oxygen can be arranged by contract. The greater the volume used, the lower its unit cost. The transportation of oxygen from the factory may be a big item.

SUMMARY

Peripheral circulatory failure featured by many of the phenomena of shock, including tachycardia, low venous pressure and hemoconcentration, is the usual mode of death in pneumonia.

Among the factors making such a termination more probable are dehydration, starvation and anoxemia.

A pneumonia patient should be considered a case of potential anoxemia, even if cyanosis has not proved anoxemia to be present.

Pneumonia patients should be supplied with extra oxygen so that what alveoli are functional are filled with an enriched atmosphere. The good offices of oxygen include the relief of symptoms of anoxemia, restlessness, anxiety, air hunger, loss of motor and emotional control, and even delirium.

Oxygen permits easier nursing care and better nutrition of the patient.

Oxygen minimizes the danger of circulatory failure.

At present the most widely used methods of oxygen administration are the tent and the oropharyngeal insufflation. Certain suggestions are made to make effective whatever method is used.

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SO-CALLED "UNRESOLVED PNEUMONIA": BRONCHOSCOPIC ASPECTS

"UNRESOLVED pneumonia" is a term which has come to be rather loosely used to designate many types of chronic pulmonary conditions. True unresolved pneumonia is, of course, a definite clinical entity in which resolution is delayed several weeks or even months following the crisis. It occurs in about 2 to 3 per cent of all lobar pneumonias. The cases we wish to present here simulate these unresolved pneumonias in many respects, but have certain clinical features that place them in a different category. These cases occur in the course of an acute upper respiratory infection and develop physical signs and symptoms which closely simulate pneumonia. On careful analysis, however, one finds the pneumonia is atypical and the recognition of the differences is of considerable clinical importance in determining therapy.

While physical findings are of prime importance, we wish to stress also the roentgen picture and the bronchoscopic findings of these cases. The interpretation of certain obscure x-ray findings is frequently facilitated by the examination of the bronchus leading to the area in question. The addition of bronchoscopy to the armamentarium of the physician treating pulmonary conditions has permitted him to see the living pathology and apply therapeutic measures directly to the lesion.

The following 3 cases are typical of these so-called "unresolved pneumonias." They occur in the course of an upper respiratory infection, simulate pneumonia, but the pathogenesis, pathology, course, and treatment are quite different.

Case I.—This thirty-four-year-old woman was entirely well when she developed an upper respiratory infection about the 10th of December. Its onset was no different from occasional other "colds" she had had, and consisted of a cough, sore throat, purulent nasal discharge, headache, malaise, and fever which several times reached 102° F. Symptoms subsided within a week, so the day her temperature returned to normal she was up and about. The next day she had a rather severe chill which was followed by a rise in temperature and a return of her persistent cough. During the next week her daily temperature rose from normal to 103° or 104° F., the rise being preceded by a chill and followed by profuse diaphoresis. Her cough was always productive of a thick yellow sputum, most copious during the height of the temperature. The remainder of the history, while carefully studied, was essentially negative for information relative to the present discussion.

Physical examination on admission, two weeks after onset of the illness, revealed a rather acutely ill, pale, thirty-four-year-old female, who was perspiring profusely. She coughed frequently during the examination and was slightly dyspneic. Essential findings were limited to the chest, although one carious tooth with pus exuding from the gingival margin should be noted. Inspection revealed a slight limitation of motion of the left side of the chest. Resonance was normal throughout the right side, but dull on the left side posteriorly from the level of the angle of the scapula inferiorly. Breath sounds over this area were by no means constant. At times they were completely absent, while at others distinct exquisite bronchial breathing was noted, associated with bronchophony and bubbling râles. The heart borders were shifted slightly to the left, the left border being 1 cm. to the left of the midclavicular line and the right border entirely under the sternum. There were no thrills, rhythm and rate were essentially normal, but there was a slight soft systolic murmur. The urine was essentially negative, the red count going down steadily and the white count rising. Agglutination tests for typhoid and undulant fevers were negative, and blood smears taken during the chills were negative for malaria. Because of the constant dullness in the left lower lobe, paracentesis had been done, which was also negative.

A diagnosis of resolving left lower lobe pneumonia was made on admission, because of the physical findings of consolidation in this area. Roentgen ray examination was reported as follows: "There is intensification of parenchymal markings throughout both lung fields with a hizarre grouping in the left lower lobe and a suggestion of a compression of linear striations. The entire area has a slight fuzzy appearance. The cardiac shadow is entirely to the left of the spine shadow, an unusual position. Examination in the left oblique exhibits a soft cloudiness in the left base, more marked in the hilar region. The unusual cardiac position and the soft-mottled fuzziness suggest primarily a partial atelectasis of the left lower lobe, with incomplete resolution of a pneumonic process and allied possible changes as a secondary consideration."

During the week following admission to the hospital her clinical course was definitely down hill. The temperature reached a peak of 104° F. daily, and she became considerably weaker.

At that time the following note was made: "The patient's clinical course

is that of an upper respiratory tract infection with a pulmonary complication which has not advanced to complete resolution. The physical findings show a heart which is not enlarged, is normally located, and which has a systolic murmur at the apex with an occasional extrasystole. The left lower lobe posteriorly shows an area of impaired resonance over which breath sounds can be heard. Many râles are present on deep inspiration and voice sounds are muffled. This would indicate that the area is within the lung. For the present the area would be regarded as one of unresolved bronchopneumonia."

With the continuation of symptoms and no change in the physical findings, inspection of the bronchus leading to the involved area seemed advisable. Bronchoscopy revealed an essentially normal trachea and right bronchus, but the mucosa of the left side was thickened and red. The orifice of the bronchus leading to the posterior division of the left lower lobe was stenotic, intensely red, and almost occluded by inflammatory swelling. Thick, white, tenacious pus exuded or oozed from the bronchus. This was aspirated, the bronchus dilated with forceps, and cocaine applied to shrink the mucosa.

The day preceding bronchoscopy the patient's temperature had risen to 105.4° F., and two hours following bronchoscopy it again reached 105° F. The next day its peak was 102° F. and within four days it dropped below 100° F. The bronchoscopy was repeated a week later and considerably more pus aspirated, after which the temperature returned to normal. Her general condition improved following the first bronchoscopy, but the physical findings did not change markedly until after the second aspiration when the dulness and bronchial breathing diminished. Further roentgen studies showed the heart and diaphragm returned to their normal positions, and the density in the region of the left lower lobe disappeared. The linear striations of the bronchi back of the heart remained accentuated, however, but the injection of iodized oil showed no evidence of bronchiectasis.

This case presents the typical picture of an upper respiratory infection complicated by an atelectasis of a portion of a pulmonary lobe. The findings on physical examination suggested a pneumonia, but the temperature, ranging from subnormal to above 104° F. each day is not typical of pneumonia. Similarly, the shift of the heart, exaggerated bronchophony and exquisite bronchial breathing are not as pronounced in pneumonia as they are in these atelectatic areas. Finally, the bronchoscopic picture of an inflamed, stenotic bronchus, completely occluded with pus, proved that air was not entering that portion of the lung.

Case II.—This sixteen-year-old girl had had a productive cough, hemoptysis, and night sweats for the eight weeks prior to admission to the hospital. She lost 22 pounds during that time. Two weeks before the onset of symptoms her sister had had "flu" with a dry unproductive cough, and the

patient's symptoms started with a "cold" she believed she had contracted from her sister. Careful analysis of her history while at home made it apparent that she had been quite acutely ill, with a high temperature, and during the first three weeks of the illness had raised bright blood clots and blood-tinged, foul, purulent material—always more than a cupful a day. Four weeks before admission she had pitting edema of the ankles, and her eyelids were puffy.

Her past history is interesting in that she had a similar but much milder attack two years before the present one, at which time the roentgen examination showed an essentially normal chest.

Physical examination revealed a thin, pale, white female, sixteen years of age, not acutely ill but rather toxic. Considerable purulent secretion was found

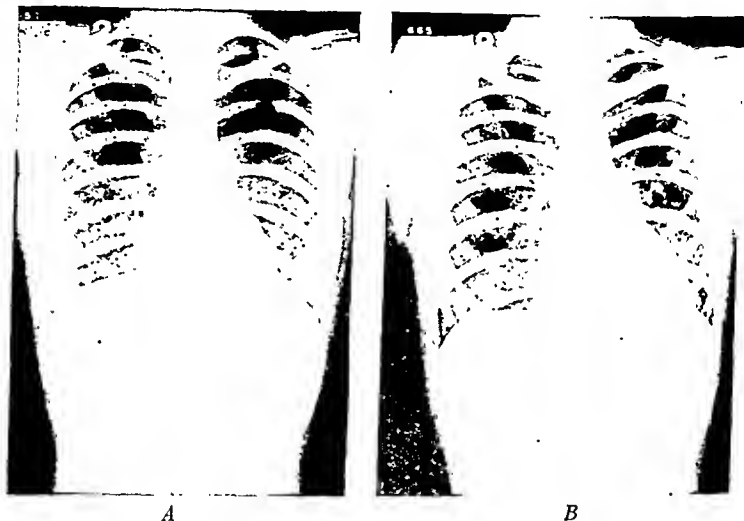


Fig. 21.—Case II. *A*, Roentgenogram two years previous to onset of present illness showing an essentially normal chest at that time. *B*, Roentgenogram eight weeks after onset of present illness demonstrating the elevation of the left diaphragm and the shift of the heart toward the left associated with the atelectasis of the posterior division of the left lower lobe.

in the postnasal space running down the posterior pharyngeal wall. There was a slight limitation of motion of the left side of the chest, decreased fremitus and dullness over the left base posteriorly, and markedly diminished to absent breath sounds over that area. Following cough, râles could be heard throughout the left chest. The heart rate was rather rapid, 112, but regular, and there were no murmurs. The apex beat was in the anterior axillary line, and on percussion the entire heart was found shifted to the left, no dullness being found to the right of the sternum. The remainder of the physical examination was essentially negative. The roentgen ray examination confirmed the physical findings of the shift of the heart and mediastinum slightly to the left, and demonstrated an elevated left diaphragm. The left costophrenic angle was

partially obliterated by a rather homogeneous density which occupied the distribution of the left lower lobe.

The admitting diagnosis in this case was unresolved pneumonia, but in view of the findings in the previous case it was suggested that this might be an atelectasis due to an inflammatory bronchial stenosis secondary to an upper respiratory infection. Bronchoscopy revealed the larynx, trachea and right bronchus to be normal. The mucosa of the left side, however, was red, thickened and friable, and the lower lobe bronchus was occluded by a considerable amount of thick, white, tenacious secretion. The process did not appear to be localized to any particular branch bronchus as in the previous case, but to extend throughout the entire lower lobe. Secretion was aspirated and the area cocainized with 10 per cent cocaine. The aspirated material con-



FIG. 22. Case II. Bronchography, anteroposterior and left lateral, demonstrating the dilatation of the left lower lobe bronchi.

tained a very hemolytic type of streptococcus in pure culture. There were no acid fast organisms.

Repeated bronchoscopic aspiration once or twice a week for a period of six months finally resulted in an almost complete re-aeration of the lung. Pneumothorax shows a definite dilatation of the bronchi back of the heart. It might be mentioned that sulfanilamide did not improve the condition, but that a very recent scarlatinal serum had a definite effect in decreasing the toxicity.

This patient's illness was of considerably longer duration before bronchoscopic aspiration than that of the previous case. The process was more extensive, and while she was not as

acutely ill as the first patient, she had an associated nephritis which time does not permit us to discuss here. Her cough was looser following the first bronchoscopy, and postural drainage at frequent intervals aided her in raising the tenacious material. In view of the much longer course of the illness in this patient and because of a previous negative chest x-ray, it is interesting to note that visualization of the bronchi by means of iodized oil demonstrated definitely an early bronchiectasis.

Case III.—This junior medical student, twenty-three years of age, was admitted to the hospital acutely ill complaining of chills, fever, muscular aches and pains of only two days' duration. He had an irritating type of cough which was only occasionally productive, and which was accompanied by considerable chest pain. Physical examination showed a slight limitation of motion of the left side, dullness and decreased fremitus at the left base posteriorly, and almost absent breath sounds over this area. While a provisional diagnosis of pneumonia was made, further examination the following day suggested that the heart and mediastinum were displaced to the left, but the roentgen ray examination was as follows: "Fluoroscopy and films made in P-A and left lateral projection showed a diffuse density over the area corresponding to the left lower pulmonary lobe. There is no evidence of mediastinal shift or elevation of the left diaphragm at this time. The findings are considered consistent with lobar pneumonia."

One week after admission he was slightly better, but while his temperature had receded from 103 to about 100, it was rising again to its former level. His paroxysms of cough were productive of gray sputum flecked with blood, his throat became red and sore, and three days later he developed a scarlatiniform rash. It is significant to note that the rash appeared ten days after the onset of the illness. Dullness and diminished tactile fremitus continued to be present over the left lower lobe posteriorly, and definite amphoric breathing with whispered pectoriloquy developed in an area 8 cm. in diameter just below and lateral to the tip of the scapula. The apex heat was definitely beyond the nipple line. With these findings a diagnosis of postpneumonic lung abscess of the left lower lobe was made. In view of the fact that hemolytic streptococci were found in the throat smear and in the sputum, convalescent scarlet fever serum was given.

Two days following, with findings essentially the same on the left side, he developed somewhat similar signs on the right, but to a much less marked degree. These consisted of moderately impaired resonance posteriorly with distant bronchial breathing about the level of the ninth rib. They disappeared within a few days.

Following 4 injections of 20 cc. of the convalescent scarlet fever serum intravenously the patient's general condition improved, and he desquamated on his hands and feet three weeks later. His temperature returned to almost normal, but his cough continued to be productive, and he raised white purulent material. Physical findings indicated the process in the left chest showed little

tendency to clear, and at this time roentgen ray examination confirmed the presence of an atelectatic left lower lobe; the heart was now displaced to the left, and the left diaphragm elevated. Bronchoscopy was done seven weeks after the onset of the illness. The larynx, trachea, and right bronchus were normal. The left side, however, showed considerable distortion. There was an ulcerated area along the medial wall of the left main bronchus, and considerable stenosis of the orifice of the posterior division of the lower lobe bronchus. The tenacious, purulent secretion oozed from the stenotic bronchus without bubbling. Shrinking the mucosa with cocaine and dilating the orifice with forceps and the tube mouth resulted in liberating quite a bit more of the secretion. The culture of this secretion showed it to be a pure growth of hemolytic streptococci.



Fig. 23.—Case III. Iodized oil instilled into the left lower lobe bronchus showing questionable dilatation of the bronchi behind the heart. Note the marked shift of the heart to the left and the elevation of the left diaphragm.

Bronchoscopic aspiration was repeated three times during the following two weeks, and on each examination a diminution of the amount of secretion as well as degree of inflammation of the left lower lobe bronchus was noted. Physical findings improved markedly and roentgen ray showed a re-aeration of the involved lobe. At this time the injection of iodized oil in the left bronchial tree by the catheter method showed a questionable cylindrical dilatation of bronchi behind the heart.

This patient had a typical atelectasis of the left lower lobe following an inflammatory occlusion of one of the larger bronchi. He apparently had a similar area in the right side which was smaller, and which disappeared spontaneously within

a short time leaving no residual findings. While his scarlet fever rash appeared ten days after the roentgen examination of the chest revealed pulmonary pathology, the organism subsequently cultured from the bronchus was the hemolytic streptococcus. Cough and physical findings disappeared after the third bronchoscopy, and a recent x-ray, six weeks after the illness subsided, is entirely negative. Both the heart and diaphragm have returned to their normal positions.

These 3 cases are typical of a group of cases frequently termed "unresolved pneumonias." While they simulate pneumonia at the onset, they are, in reality, cases of pulmonary atelectasis occurring during the course of upper respiratory infections. In each instance the pathology was limited to the left lower lobe, or a division of the left lower lobe. Other cases could be added in which the right middle or lower lobes have been involved, but time does not permit. The atelectasis in these cases occurs as the result of an inflammatory stenosis of the bronchus, with absorption of the air beyond the stenosis, followed by an increasingly severe infection due to inadequate drainage. We see this frequently in children, where a very small degree of inflammation can readily block the tiny bronchial divisions of a child.

Most of these cases clear promptly, spontaneously or after the use of expectorants. Postural drainage is of definite value, and should be used in conjunction with the other methods of therapy, not substituted by them. *When drainage is inadequate, however, and symptoms persist, bronchoscopy should not be delayed.* Prompt relief of symptoms and clearing of the lesion follows bronchoscopic aspiration in those cases that are bronchoscoped early in the disease. We have noted repeatedly, on the other hand, that in those cases in which the lung remains atelectatic over a longer period of time, it requires an actual and even proportionately longer period of time to re-aerate the lung. The cases presented here demonstrate this point clearly. The first case, bronchoscoped early in the course of the disease at a time when the patient was extremely ill, with a temperature above 105° F., had a rather spectacular drop in temperature following aspiration and bronchial dilatation. Her general condition showed just as marked a change,

and she had only one slight chill a week later. Because of it we felt that bronchoscopy was again indicated. Following the second bronchial aspiration symptoms subsided completely. The point I wish to emphasize is that the factor responsible for this general improvement, prompt, adequate drainage, resulted also in a rapid return of function to the atelectatic lobe. Physical examination following the first bronchoscopy demonstrated that air was entering this area to some degree, and entered it freely after the second aspiration. These findings were confirmed by x-ray, which showed the heart shifted back to its normal position. This is in contrast to the second case in which symptoms indicate the atelectasis was present at least two months before bronchoscopic drainage was established. While repeated bronchoscopies resulted in an almost complete reaeration of the lung, it has been a long, slow process with definite indications that some degree of permanent damage has taken place.

Comparative studies of the bronchographies of these 3 cases illustrate another extremely important point. In the first case, with early reaeration of the lung, x-ray, following the instillation of iodized oil into the left lower lobe bronchus, demonstrates that the bronchi have remained or returned to normal size and distribution. In the second case, however, the bronchography is quite different, showing considerable dilatation of the bronchi behind the heart. From the history we know that two months elapsed between the onset of symptoms and the time drainage was established. Physical and x-ray findings indicate that reaeration was accomplished very slowly, requiring another two months. During this time bronchiectasis has apparently developed in this area. Bronchography in the third case shows a "questionable cylindrical dilatation of bronchi behind the heart," placing this case between the first and second in degree of residual pathology. With this in mind, we note that it falls between the first and second in regard to time between the onset of the illness and the establishment of adequate bronchial drainage. And, finally, reexpansion of the lung was not as prompt in this third case as in the first, but much quicker and more complete than in the second.

Thus, in these 3 cases of atelectasis occurring in the course

of an upper respiratory infection we note that the time required to reexpand the lung as well as the degree of permanent damage (bronchiectasis) present after reexpansion are both proportional to the time the lung remained atelectatic.

SUMMARY

1. Atelectasis occurring in the course of an upper respiratory infection often simulates a pneumonia that fails to go on to resolution. These cases are generally termed "unresolved pneumonia."

2. Unresolved pneumonia is a real entity, but these cases are definitely different, requiring an entirely separate therapeutic régime.

3. Simple cases of atelectasis get well without diagnosis, following the use of expectorants and postural drainage.

4. If the physical and roentgen findings persist, early bronchoscopic aspiration results in a rapid relief of symptoms, disappearance of physical signs, and reaeration of the atelectatic portion of lung. In cases of longer duration, however, reexpansion of the lung is not as prompt.

5. The degree of residual permanent damage (bronchiectasis) following atelectasis is dependent upon the length of time the lung remains collapsed. Therefore, bronchoscopic aspiration should be instituted early in an effort to keep the bronchial tree free of pus, and to prevent bronchiectasis from developing in the area of atelectasis.

CONTRIBUTION BY DR. AUSTIN A. HAYDEN

ST. JOSEPH'S HOSPITAL

ZINC SULFATE INTRANASAL SPRAY TECHNIC IN POLIOMYELITIS PREVENTION

FOLLOWING the articles by Schultz and Gebhardt¹ of Stanford University, and Peet, Echols and Richter² of the University of Michigan, the zinc sulfate intranasal spray was employed at St. Joseph's Hospital during the Chicago epidemic in the month of September as part of the prevention program of the Chicago Board of Health.

One hundred ninety-eight children were given 416 treatments; 77 received one treatment, 24 two, and 97 three treatments on alternate days. One hundred of these children returned for check-up four weeks later.

Before beginning the treatment the consent of the parent was secured in each case in the presence of 2 witnesses. It was carefully explained to them that the likelihood of their children developing poliomyelitis was extremely slight, inasmuch as there were comparatively few cases in Chicago, and secondly, that the sense of smell would be destroyed most likely temporarily. The parents were all desirous of giving their children the benefit of this prevention.

On admission to the hospital a brief history was taken, covering age, sex, date of birth, name of family doctor, temperature, and exposure to the disease. The following technic was employed:

The child's nose was examined for gross obstructions, then packed with cotton soaked in a solution of 2 per cent cocaine with 10 drops of adrenalin to the ounce. The packing was

¹ Schultz, E. W., and Gebhardt, L. P.: Zinc Sulfate Prophylaxis in Poliomyelitis, *J.A.M.A.*, 108: 2183 (June 26), 1937.

² Peet, Max M., Echols, Dean H., and Richter, Harry J.: The Chemical Prophylaxis for Poliomyelitis, *ibid.*, p. 2184.

allowed to remain for ten minutes. The solution used for spraying consisted of 1 per cent zinc sulfate in five tenths of 1



Fig. 24.—Introducing nasal packs.



Fig. 25.—Spraying.

per cent sodium chloride. The head was tipped far back and held by an assistant. A special DeVilbiss long tip atomizer,

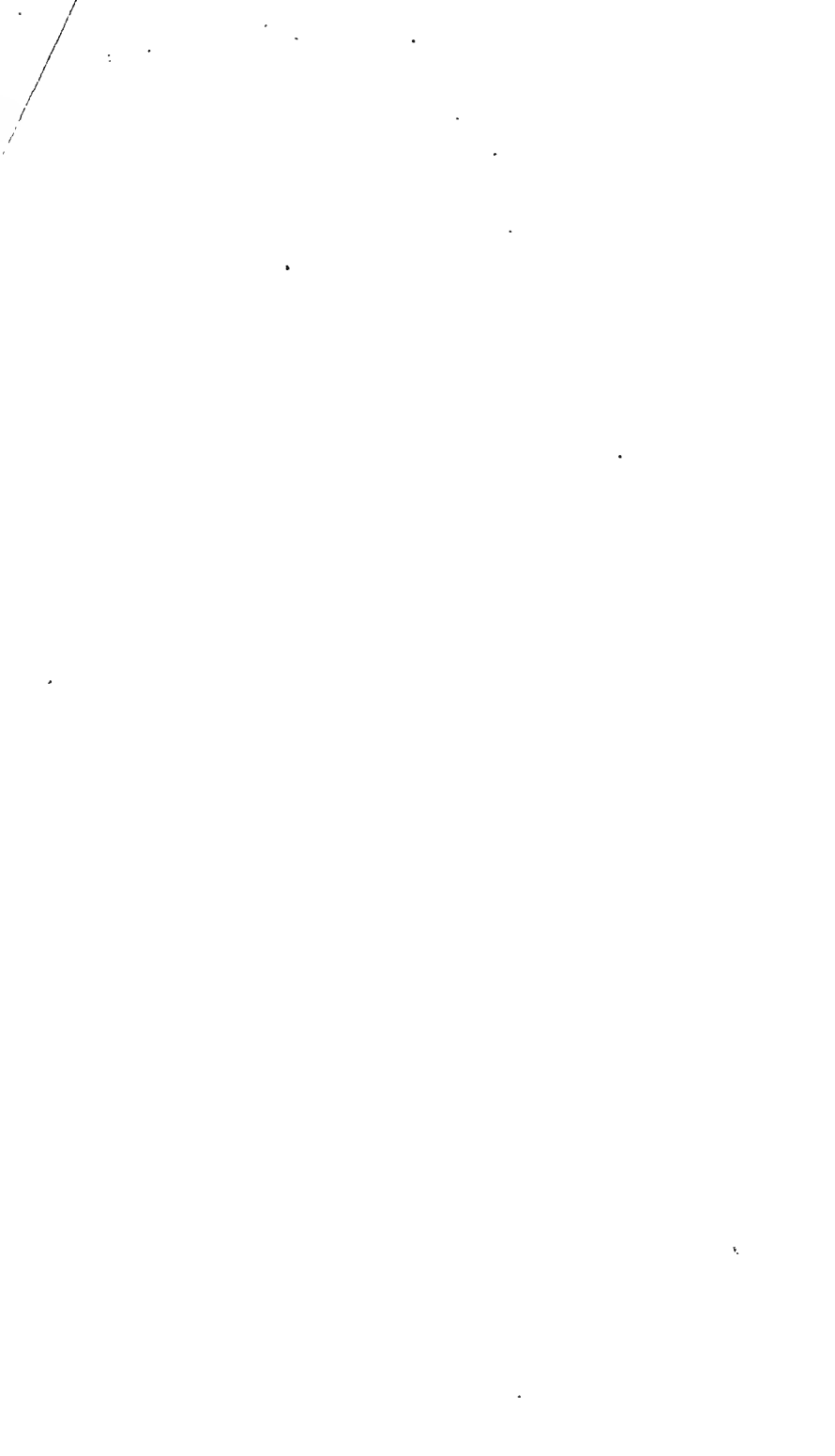
such as recommended by Peet, was employed. The atomizer was held very carefully against either the lip or chin with the ring finger of the right hand so that the tip did not puncture the walls of the nose, and great care was exercised in inserting the tip along the septum so as not to catch it under the turbinates. Approximately 1 cc. of the zinc solution was used on each side.

Very little difficulty was experienced in getting the children to submit to the treatment. The older ones were taken first to allay the fear that some of the smaller children were inclined to exhibit.

After the routine became established it was possible to take care of 60 children an hour. Only once was it necessary to use the recovery room which the hospital had provided for children showing unusual reactions. Only 7 children had nose-bleeds following the spray and none of these were severe. Ninety-seven per cent showed anosmia lasting from a few hours to a few days.

In the check-up after four weeks no reaction was noted in any of the cases sprayed. The parents cooperated willingly; there were only 3 children, 2 in one family, whose parents objected to bringing them back for final observation. None of the 198 children so treated contracted poliomyelitis. In this comparatively small group the results, of course, are not conclusive.

This is a procedure that can be easily carried out in the private office of any otolaryngologist.



CLINIC OF DR. WALTER WILE HAMBURGER

MICHAEL REESE HOSPITAL

THE HEART IN INFLUENZA

IN Thomas Sydenham's¹ account of influenza in 1679, no mention is made of involvement of the heart. Since that early day, up to and including the present, considerable divergence of opinion exists concerning this problem. It will be the purpose of this brief discussion to weigh the evidence for and against the thesis of cardiac involvement in influenza, evidence gleaned from the literature and from my own personal experience.

Examples of this divergence of opinion taken from the literature may be seen in Robert Babcock's² statement in 1908: "The injurious influence of influenza upon the heart muscle is a matter of every day observation. Not only is the functional integrity of the organ disturbed in the course of influenza, but signs of cardiac inadequacy may develop a considerable time after the disappearance of la grippe."* Henry Christian³ on the other hand writing of his own experiences in the 1918 pandemic observed that, "cardiac complications are infrequent, . . . clinically detected pericarditis is infrequent. Acute endocarditis is rare . . . recognizable myocarditis is a great rarity. Chronic cardiac disturbances following influenza are very infrequent. All in all, the heart bears a remarkable immunity to lesions following influenza."†

James Mackenzie's⁴ views, quoted by MacNalty and Malloch in 1920, are characteristically conservative and philosophical: "Mackenzie has given an excellent picture of the heart in influenza. Unless pericarditis or endocarditis occurs, he is

* Babcock, Robert H.: *Osler's Modern Medicine*, vol. IV, p. 90, Lea and Febiger, Publishers.

† Christian, Henry: *Oxford Medicine*, vol. 14, p. 844, Oxford University Press, Publishers.

TABULATION
INVOLVEMENT OF THE HEART IN INFLUENZA

Author.	Date.	Type of involvement, pathology, symptomatology.	Time of involvement.	Frequency.	Duration and prognosis.
Robert Babcock ²	1908	Disturbances of functional integrity.	Early and late.	Frequent.	
Ludolph Krehl ³	1913	Parenchymatous changes in myocardium. Irregularities, dilatation, dyspnea, palpitation, angina.	Early and late.	Quite frequent.	Not particularly favorable.
Alfred Stengel ³	1918	<i>Epidemic of 1889:</i> Arrhythmia, bradycardia, Tachycardia, older patients. <i>Epidemic of 1918:</i> Bradycardia, extrasystoles, auricular fibrillation, frequent syncopal attacks.	Little early. Frequent sequelae. Fatal syncope during convalescence.	Not frequent. Not frequent.	
W. W. Hamburger ¹	1920	Acute parenchymatous degeneration and vacuolization of the myocardium.	Early and late.	Not frequent.	Fatal and nonfatal cases. Complete recovery in majority of nonfatal cases.
With W. S. Priest, Jr. ³	1923	Arrhythmia, partial heart block. Auricles and conduction pathways involved.			
Ernst Romberg ³	1921	Functional (toxic) involvement of heart muscle. Marked dilatation.	Arrhythmia, extrasystoles, conduction disturbances during height of fever.	Frequent convalescent heart weakness; anginoid attacks, bradycardia, vertigo.	Few days or weeks to several years. Most severe in previously damaged hearts.
Henry Christian ³	1921	Pericarditis, endocarditis, myocarditis, chronic cardiac disturbances all rare and infrequent.	Infrequent. Heart remarkably immune to influenza.	
James Mackenzie ⁴	Slight dilatation, systolic murmur. Breathlessness, angina, palpitation, expression of general exhaustion.	Early during height of fever.	Infrequent.	Good.

<i>Hugo Rother¹⁰</i>	1924	Endocarditis, (Also Libman and Horder.)			
<i>Ernst Felsen¹¹</i>	1929	Endocarditis. Myocarditis.	1.2 per cent. Seldom. May vary in different epidemics.	
<i>Paul D. White¹²</i>	1931	Occasional acute and subacute bacterial endocarditis, pericarditis.	Late weakness and cardiovascular symptoms due to marked effort syndrome.	More frequent than following pneumonia.	Weeks or months.
<i>Harlow Brooks¹³</i>	1933	Myocardial degeneration most common; Occasionally true myocarditis; occasional terminal coronary thrombosis.	Serious cardiac disease frequent.	Sudden death. Chronic tripping of heart.
<i>William J. Kerr¹⁴</i>	1934	Bradycardia. Diminution of heart sounds in fatal cases. Cyanosis.	Early or late. After acute stage marked, vagal tone, bradycardia, sinus arrhythmia, extrasystoles.	Fatal cases with extensive pulmonary edema and cyanosis.

of the opinion that the effect of influenza on the heart, is just that which is so well recognized in any other febrile affection; it may become slightly dilated and a systolic murmur appear, but matters generally soon right themselves shortly after the cessation of the fever. Throughout his very wide experience of cases of myocarditis leading to heart failure, it is gratifying to learn that he could never say definitely that any attack of influenza was the cause. Most of the symptoms complained of by patients after an attack of influenza, such as breathlessness on exertion, precordial distress or pain, and palpitation, are in his opinion but an expression of a general exhaustion resulting from a severe infection.”*

Other brief quotations from the literature are similarly of interest. To the end that these divergent viewpoints may be readily classified and contrasted, I have collected them in the simple table (pp. 112–113). The author, date, type of heart involvement, time of involvement, frequency, duration, prognosis are tabulated so far as data is available. Study and analysis of this material reveal some interesting results.

It seems clear that the upper respiratory infection we recognize as influenza *may* cause some type of heart involvement. All observers seem agreed on this point. Other details of this involvement, however, are the subject of wide differences of opinion as may be seen from the table. Under the heading “type of involvement,” one is early impressed by the variety of opinions expressed, although there remains some agreement as gauged by the frequency of certain findings. Under pathology, myocardial parenchymatous changes and cardiac dilatation are mentioned three times; endocarditis and myocarditis twice; pericarditis, acute and subacute bacterial endocarditis and terminal coronary thrombosis once each. Under symptomatology, arrhythmia and tachycardia are each noted four times; extrasystoles, angina or anginoid symptoms three times; dyspnea, palpitation, conduction disturbances, functional disturbances twice each; tachycardia, auricular fibrillation, syncope, vertigo, cyanosis once each.

From the above data, which includes and coincides with

* Mackenzie, James: Nelson's Loose-Leaf Medicine, vol. I, p. 621, Thomas Nelson and Sons, Publishers.

my own views, one may trace a composite picture of the involvement of the heart in influenza with a fair degree of accuracy. At the bedside of a patient suffering with influenza, apart from the obvious symptoms of an acute upper respiratory illness—fever, flushed face, injected conjunctivae, headache, generalized aches and pains, restlessness, general discomfort—one may be first impressed with some degree of cyanosis and some disproportion between the heart rate and the temperature level—a relative bradycardia. During the height of the infection or during convalescence certain irregularities of the pulse may appear, extrasystoles, marked sinus arrhythmia, dropped beats, partial or complete heart block—rarely auricular fibrillation. The patient, depending on his sensitivity threshold and the degree of toxemia, may be totally unaware of these cardiac disturbances, or may complain of palpitation, precordial distress, thumps or twists in his chest, dyspnea, etc. In the days and weeks, rarely months and years following the acute disease, profound exhaustion, easy fatigue, extreme weakness, dyspnea, palpitation, anginoid pain may continue as distressing complaints. Vertigo, syncope, coronary thrombosis, unexpected death occur more rarely.

The pathology responsible for this clinical picture is somewhat uncertain and indefinite. That toxic myocardial parenchymatous changes may occur and particularly with more severe and fatal cases seems clear. That these structural changes may completely disappear following subsidence of the acute infection seems equally clear. On the other hand, particularly in older individuals and those with previously damaged hearts, complete resolution may not occur. In such patients, evidence of permanent cardiac damage, influenzal in origin, may be found, if earnestly and critically sought for—evidence in the patient's history, physical examination, size and position of the heart, clarity and character of the heart sounds, x-ray of the heart, electrocardiogram, response to effort, blood pressure, etc.

Much less frequent than involvement of the heart muscle and conduction pathways, are the rare cases of influenzal endocarditis, pericarditis, and acute and subacute bacterial endocarditis. In these patients virulent pathogenic influenzal bacilli have been found, organisms, one judges, which are the

exception rather than the rule in the epidemics and pandemics of influenza. Probably, also, certain of these more severe organic involvements of the heart's anatomic structure are doubtless due to the association of secondary invading organisms, hemolytic and nonhemolytic streptococci, viridans organisms, possibly staphylococci and others.

As to the time in the course of the disease in which cardiac involvement occurs, most authors are in agreement that this may become evident symptomatically, both early and late. Early, various conduction disturbances, arrhythmias, extrasystoles may be found; late, various cardiac sequelae, fatal syncope, convalescent heart weakness, anginoid attacks, extreme bradycardia, vertigo, marked effort syndrome, prolonged exhaustion have all been described. In general one concludes that the late influenzal sequelae—the cardiac harvest—are more frequent, more distressing, and demand the most discerning analysis and care.

There are several explanations for the discrepancy in opinions of clinicians of equal experience and competency concerning the frequency and severity of involvement of the heart in influenza. The first of these explanations centers around the fact that compared with the frequency of heart damage in such well recognized infections as acute rheumatic fever, syphilis, diphtheria, influenzal involvement is undoubtedly *infrequent*. Secondly, the influenzal cardiac harvest varies from epidemic to epidemic, pandemic to pandemic, and during the course of any one epidemic or pandemic. Thirdly, the cardiac sequelae may be so transitory, mild, or occur so late in convalescence, they are likely frequently missed.

Duration and prognosis of postinfluenzal cardiacs? Here again one finds great divergence of opinion. In my own follow-up studies of 8 patients with postinfluenzal cardiac disease of the 1918–1919 pandemic, 5 had completely recovered within a three-year period, 1 was unimproved, 2 could not be traced. In general, one gains the impression that the prognosis of *established* postinfluenzal cardiac disability is not particularly favorable, months or years may be needed for recovery. Chronic cardiac crippling may result, particularly in previously damaged hearts, unexpected sudden death without demonstrable cause occurs.

At this point I should like to digress for a moment from the discussion of influenzal cardiac involvement, to discuss very briefly certain newer concepts concerning the etiology of influenza. I do so, as I feel this new work may be of some importance in understanding and reconciling various divergent viewpoints concerning the rôle of the heart.

While there is general agreement as to the unity and character of worldwide pandemics of influenza, less clarity and considerable confusion exists concerning the nature of the milder, less widespread interepidemic episodes of acute upper respiratory disease. Doubtless, many of the so-called "epidemics" of influenza are either a single noninfluenzal upper respiratory infection, or a mixture of various infections; the common cold, influenzal or noninfluenzal pharyngitis, tracheitis, bronchitis, acute rheumatic fever, or some totally unsuspected unique disease entity. In this latter connection, Francis¹⁵ recent report is pertinent: "An epidemic of a mild nature which was called influenza or grippe invaded a localized area in Brazil (South America). When studies of the immunity reactions of individuals in this area were made, it was found that the disease was in fact yellow fever!"* Francis' further conclusion, which has gained support from other workers, "that one at least of the mild interpandemic diseases called influenza is casually related to a filtrable virus," is highly suggestive. Still other investigators believe both a filtrable virus and influenzal organisms are active etiologic agents. In the light of this recent work, with confusion in clinical diagnosis and newer concepts of bacteriologic etiology, it is not difficult to understand an analogous confusion in evaluating the response

* Similar confusion in the diagnosis of infectious disease is apparent through the entire course of the history of medicine. Sir Marc Armand Ruffer (Studies in the Paleopathology of Egypt, edited by Roy L. Moodie, University of Chicago Press, 1921, p. 50) makes this interesting statement: "The evidence from historical works of comparatively modern times is of little service, because as a rule the symptoms noted are indicative not of one disease, but of several. To take an example of comparatively recent times, the epidemic which devastated Athens and was graphically described by Thucydides, has been identified according to the diverse tastes of medical and other commentators as black typhus, smallpox, cerebrospinal meningitis, scarlet fever, *influenza*, and ergotism complicated with typhus."

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of any special organ or system of organs to these infective agents.

In a careful clinical and electrocardiographic study of 100 cases of influenza with particular reference to the organs of circulation, Egedy,¹⁶ in 1929, reached the following conclusions: *approximately 50 per cent of these postinfluenzal cardiac disorders have their origin in lesions of the conduction system*; two thirds of these disorders occur after the acute attack or still later during convalescence; with proper treatment, these heart findings completely disappear in from two to six weeks. He presents the following table contrasting the frequency and type of heart involvement in acute rheumatic fever, diphtheria and influenza:

<i>Acute Rheumatic Fever</i>	<i>Diphtheria</i>	<i>Influenza</i>
1. Endocardium	Myocardium	Conduction system
2. Myocardium	Conduction system	Vascular system
3. Conduction system	Endocardium	Myocardium
4. Pericardium	Pericardium	Pericardium
5. Vascular system	Vascular system	Endocardium

Here again one sees the dominance of disturbances of the conduction pathways in influenza, findings which are in accord with my published cases of the 1918-1919 epidemic.

In connection with the preparation of this paper, I recently reviewed the histories of 50 cases of acute influenza occurring during the past eighteen months, from the files of the Albert Merritt Billings Hospital, Chicago.* The majority of these patients were University of Chicago students, young men and women between the ages of eighteen and twenty-four. Their presenting complaints were strikingly similar: "cold," sore throat, generalized aching, cough, general malaise, fever, etc. There were occasional exceptions, such as epistaxis, nausea and vomiting, anorexia, sudden fatigue, insomnia. Physical findings were universally negative except for the usual evidences of an acute febrile intoxication; flushing of the face, redness of the throat, cervical adenopathy, macular rash. The expected disproportion between temperature and pulse levels was usually

* I am indebted to Dr. George F. Dick, Chairman of the Department of Medicine, University of Chicago, for his courtesy in giving me access to the medical histories of influenzal patients, from the files of the Albert Merritt Billings Hospital, Chicago.

present; temperature 102.8° F., pulse 86; temperature 100° F., pulse 60; temperature 104° F., pulse 100. A leukopenia was almost pathognomonic; 3500, 4800, 4400, 5200, 6400. In none of the 50 cases, could evidence of heart involvement be demonstrated, either by physical findings, x-ray or electrocardiogram. One twenty-three-year-old divinity student with a history of 2 previous attacks of chorea in 1923 and 1925, with a markedly enlarged heart, inactive rheumatic valvulitis, sclerosis of the mitral valve, made an uneventful recovery without apparent additional damage to his heart. With few exceptions, the acute febrile attack subsided in forty-eight to seventy-two hours. No follow-up studies of these patients has been made, so although no signs of heart disturbance were found during the febrile period, the possibility, remote perhaps, of late cardiac sequelae cannot be denied. Against this possibility, however, is the fact that the majority of these patients were members of the University Student Health Service, and had untoward symptoms developed later, they would in all likelihood have reported back to the clinic for examination.

Treatment.—Just a word as to treatment. Prompt recognition of the nature of the acute infection and immediate bed rest are important. Complete bed rest during the febrile period and for a day or two thereafter is equally important. During this time, moderate increase of fluids—water, fruit juices, milk, tea, coffee, broth, together with a soft diet are indicated. Aspirin or other salicylates are useful to add to the comfort of the patient, relieve pain and aching, perhaps to combat somewhat the fever. Codeine should be added if cough or pain are severe and distressing. If evidence or suspicion of heart involvement should arise, tachycardia, arrhythmia, dyspnea, chest pain or pressure, extreme bradycardia, increase of heart size, complete bed rest should be prolonged until all such evidence or suspicion has been resolved. In the remote event of clearly demonstrated heart muscle failure, unrelieved by prolonged bed rest, the patient should be digitalized.

To summarize very briefly my conception of the rôle of influenza in cardiac disability, I would conclude as follows: influenza, although its exact bacterial or infectious nature is not entirely clear undoubtedly, at times at least, involves the

heart. This involvement varies in frequency and severity from pandemic to pandemic, from epidemic to epidemic, during interpandemic or interepidemic periods, at different times during the course of any single pandemic or epidemic. Difficulties in clinical diagnosis contribute to the differences of viewpoint of competent observers as to the frequency and type of cardiac involvement. In general, involvement of the heart in influenza is infrequent—particularly when contrasted with the frequency of involvement in acute rheumatic fever, syphilis, diphtheria, etc. Bradycardia, various cardiac arrhythmias, partial or complete heart block, extrasystoles, dyspnea, palpitation, anginoid pain, extreme malaise and exhaustion are most frequently observed. *One may cautiously venture the opinion that disorders of the conduction pathways of the heart are as pathognomonic of influenza, as is mitral stenosis of rheumatic heart disease.** Conduction disturbances occur both early and late in the course of the influenzal infection—perhaps somewhat more frequently during convalescence. Prognosis is for the most part favorable. Cardiac sequelae usually disappear with sufficient bed rest, adequate treatment and careful supervision.

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PRIMARY CARCINOMA OF THE LUNG

PRIMARY bronchus carcinoma is extremely common. In our experience at the Cook County Hospital, it is the third most frequent type of primary cancer, being exceeded in incidence only by carcinoma of the stomach and the intestines. On our male medical service, we treated 1100 patients from January, 1935, to January, 1936, and of that number 9 patients had primary bronchus carcinoma, approximately 0.8 per cent of the entire group. Of approximately 67,000 general admissions, medical and surgical, in the entire hospital in 1935, there were 104 with pulmonary cancer.

As in most large series of reports our records also indicate a predominance among the male, usually up to about 80 per cent. There is no evident explanation for this preponderance except that men are possibly exposed to greater hazards in the industries, and smoke more than women.

Lung cancer has shown a large increase during the past three decades—an increase that may be real as well as apparent—and autopsies actually show an increase above that disclosed by investigation of previous years. Explanations offered to discount this as only an apparent increase include greater care and skill in physical diagnosis, and more searching laboratory investigations. The longevity of the present era may favor the increase of pulmonary neoplasms. There is, perhaps, greater exposure to irritating vapors of modern industry. Increased use of tobacco is mentioned as the cause of this large incidence, since about 70 per cent of the neoplasms occur in smokers. Chronic infection in the pulmonary

tree very seldom precedes carcinoma and is apparently a negligible etiologic factor. Despite the foregoing reasons given, no adequate explanation has as yet been offered to explain any increase in the number of cases.

Case I.—R. W., forty-three years of age, a steel worker by occupation presents very vividly many of the protean features of this disease. He was admitted June 1st, with a history of a fracture of the right forearm sustained April 23rd, following an injury while at work. He was hospitalized and treated



Fig. 26.—Patient R. W., pathologic fracture of the upper third of the right radius.

by the industrial surgeon. However, the result was unsatisfactory, and because of a persistent cough, on May 27th a chest plate was taken which showed "marked cloudiness and mixed infiltration of the right apex and intraclavicular area, extending upward from the hilum. Conclusion: active pulmonary pathology, undoubtedly tuberculosis." He was then sent to the Cook County Hospital, where a history of a cough of three months' duration was obtained. This cough was persistent, worse at night, associated with a slight amount of sputum which three weeks previously was definitely blood-tinged for several days. There had been a constant boring pain in the right upper chest which was more severe at night; he had a weight loss of 25 pounds in the past six months;



Fig. 27.—Patient R. W. right upper lobar lesion as seen June 6th.



Fig. 28.—Patient R. W., July 9th. Right upper lobar lesion with right hilar extension, atelectasis of the right lung with elevation of the right diaphragm and traction of the heart toward the right.

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Fig. 27.—Patient R. W. right upper lobar lesion as seen June 6th.



Fig. 28.—Patient R. W., July 9th. Right upper lobar lesion with right hilar atelectasis of the right lung with elevation of the right diaphragm and traction of the heart toward the right.

sleep was interfered with by the cough and pain, and weakness was a major complaint. The past history revealed lues in 1913 with apparently adequate treatment, and pneumonia in 1915. No other essential facts were elicited on thorough questioning.

A complete physical examination revealed the following significant evidence: temperature 101° F., pulse 96, respiration 28, blood pressure 150 over 80, marked dulness with distant and feeble breath sounds were noticed over the right upper lobe anteriorly and posteriorly. Over this area on the anterior surface of the chest the heart sounds and particularly the aortic second sound



Fig. 29.—Patient R. W., August 1st. Iodized oil injection reveals complete obstruction of right main bronchus with atelectasis of right lung. The heart is displaced very pronouncedly to the right. On thoracentesis no fluid was obtained.

were distinctly audible. The heart boundaries and sounds were not changed. Abdominal examination was negative. The urine revealed normal findings. The blood examination showed moderate secondary anemia and a negative Kahn. The x-ray of the chest on June 5th showed an infiltration in the upper third of the right lung field with several calcified lesions in the right hilum. The pulmonary pathology appeared to be tuberculosis. The right forearm roentgenogram revealed a pathologic fracture of the upper third of the right radius.

Progress of the disease became very rapid. Atelectasis of the right lung

with elevation of the diaphragm on the right side and deflection of the heart to the right became apparent—evidence of a chronic active massive collapse of the right lung. Bronchoscopy on July 1st revealed an infiltrative lesion opposite the tracheal bifurcation and in the right middle bronchus, but the biopsy revealed necrotic tissue with no evidence of malignancy. The x-ray of the chest

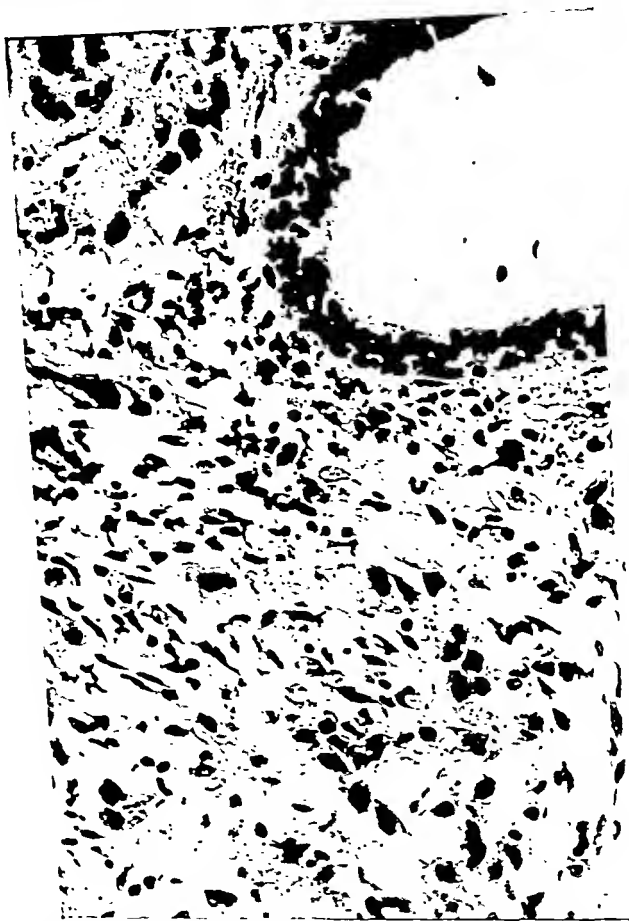


Fig. 30.—Patient R. W., bronchoscopy biopsy. Note metaplasia of normal cylindrical epithelial, single-cell lining of the bronchus mucosa into multiple layered squamous cells with infiltrating anaplastic noncornifying squamous carcinoma cells.

now shows complete consolidation of the right upper lobe compatible with the diagnosis of primary carcinoma of the lung. The bronchoscopy biopsy on July 14th revealed diffuse infiltrating anaplastic squamous-cell carcinoma. Metastases had now appeared in the anterior abdominal wall and the right lower ribs anteriorly.

Case II.—V. C. S., sixty-five years of age, entered with complaint of pain of three weeks' duration in the left leg and thigh, and a cough of four months' duration. Patient was perfectly well up to ten months previous, with no history of any respiratory disturbances. On physical examination, there was dulness in the lower right axillary region, with increased breath sounds over both lungs. The chest was somewhat emphysematous. There was impaired resonance over the right lower lobe posteriorly. In the main, there was a marked paucity of findings, and this, with the x-ray findings of July 26, 1934, which showed a marked infiltration in the base of the right lower lobe, suggested a diagnosis of primary carcinoma of the lung. x-Ray of the gastro-intestinal tract at this time was negative.

Bronchoscopy on September 17, 1934, revealed a narrowing of the middle lobe bronchus with slight thickening of the mucosa. At that time there were physical signs of a partial consolidation of the right middle lobe. The patient was steadily growing weaker. His chest wall was retracted over the right base. The intercostal spaces were definitely narrowed, and the venules on his chest wall were unduly prominent. Large, firm, discrete and confluent masses were palpable in the left lower quadrant of the abdomen. The red blood corpuscle count was 3,000,000 and the hemoglobin 60 per cent. The patient went gradually downgrade and died March 14, 1935, eight and one-half months after entrance, and one and one-half years after the onset of symptoms.

The autopsy was performed by Dr. Jaffe and revealed an adenocarcinoma of the right lower lobe (peripheral type) with metastases to the left ventricle and the muscles of the anterior abdominal wall. There was a suppurative pericarditis as well as cardiac hypertrophy; chronic emphysema of the right upper and middle pulmonary lobes, and complete obliteration of the right pleural cavity. Hydrothorax existed on the left side. There was slight ascites, arteriosclerotic granulation of the kidneys, luetic aortitis, and nodose goiter.

Case III.—J. W., clerk, fifty years of age, entered with complaint of pain in the left chest, cough and hemoptysis of ten months' duration. He was perfectly well up to two and one-half years before the time of admission, when he had influenza and was ill for two weeks. He seemed to be in good health afterward till the spring of 1933 when he began to have a cough, fever and expectoration. In January, 1934, he developed diffuse rheumatic pains which made him very weak but did not confine him to bed. At the end of February he had knifelike stabbing pains in his chest. Hemoptysis was present in small amounts. There was dull pain in the left chest anteriorly and subternally. Dyspnea was marked. There had been a loss of 25 pounds of weight in one year. Patient drank alcohol, and used tobacco moderately. Blood pressure was 104 over 68. On examination there was a lagging of the left chest with diminished to absent tactile fremitus over the entire left chest area. There was dulness to flatness at the base. Breath sounds were absent throughout. No râles were present. We performed a number of pleural aspirations which revealed a bloody effusion in each instance. Bronchoscopic examination revealed the left main bronchus filled with a red granulomatous mass. x-Ray showed an opacity of the entire left side of the chest with definite fluid level. The

diagnosis at the time of dismissal was carcinoma of the left bronchus with atelectasis of the left lung.

Case IV.—W. L., fifty-seven years of age, was admitted December 20, 1934, with his symptoms principally mental. On examination there was slight dulness over the left upper lobe. x-Ray on January 3, 1935, revealed a localized area of consolidation in the middle third of left lung field. A diagnosis was made of primary carcinoma of the lung with metastases to the brain. On bronchoscopy, it was found that the entrance to the left main bronchus was constricted, the mucosa was red. Patient developed a bronchial pneumonia January 11 and died on January 15, 1935. There was no autopsy.

Case V.—S. S., sixty-two years of age, was admitted December 20, 1934, with complaints of cough and hoarseness of six months' duration. He stated that he got his feet wet, caught cold and continued working in spite of malaise, hoarseness, cough and expectoration and a weight loss of 35 pounds in six months. In the three weeks prior to admission, he had to quit work because of intense sticking pains in right and left chest. He had a paroxysmal cough with a blood-tinged mucous expectoration and he had pronounced weakness and dyspnea. On examination, there was marked fetor oris, and rapid, labored breathing. There was diminished fremitus over the right chest laterally from the anterior to the posterior axillary line, with flatness and many crepitant and subcrepitant râles. Hemoptysis was marked on several occasions. Our first impression was that the patient might have had a lung abscess. On January 16, 1935, the patient developed a mass over the right shoulder region posteriorly, from which was aspirated 350 cc. of dark blood. On bronchoscopic examination, there was slight amount of purulent secretion in the right main bronchus, with no other findings. x-Ray examination on December 31, 1934, revealed an opacity at the base of the right lung, suggesting fluid, and there was an increase in the hilus markings. On March 9, 1935, patient developed an anesthesia of both lower limbs, diminished reflexes, and incontinence. There was no free acidity in the gastric contents. x-Ray revealed no apparent pathology in the lower thoracic vertebrae. x-Ray of the chest on January 16th showed a dense shadow with an irregular, ill-defined border in the left hilus region. x-Ray of the stomach and duodenum were negative. February 14, 1935, an opacity was found, well-defined in outline, in the upper half of the left hilus area, with cloudiness in the right lung field. On March 9, 1935, the anterior-posterior view of the spine revealed marked compression of the fifth dorsal vertebra.

The autopsy findings revealed an anaplastic, nonhornifying, squamous-cell carcinoma of the left upper pulmonary lobe with extension into the pericardial sac and metastases to the lower portions of the lobe; thrombosis of the superior vena cava; and hydrothorax of the left side with compression atelectasis of the left lower pulmonary lobe.

Case VI.—J. U., contractor, thirty-nine years of age, was admitted January 2, 1935. The patient's complaint was pain over the right deltoid region and over the left arm extending to the fingertips, and numbness over the left

forearm involving the third, fourth and fifth fingers. Patient was perfectly well up to three weeks before admission. He had walked a long distance in a snow storm and noticed, on the following day, pain starting over the vertebral region radiating down the left shoulder and involving the fingers. He also noticed numbness from the elbow to the fingers over the lateral aspect of his forearm. The pain had become progressively worse since its onset. One week later, the pain extended from the fourth to the fifth dorsal vertebra to the right shoulder involving only the right deltoid area. Numbness was not present over this region. Numbness on the left cheek, left side of nose, and upper lip began the day before admission. Patient stated that he had no headaches, no dizziness, no tinnitus, no cough, no hemoptysis, and no thoracic pain. His past history was entirely negative. On physical examination, there were no findings except a small right hydrocele. Reflexes were normal. On January 8th, examination of the chest revealed dulness over the right apex posteriorly, with occasional fine, moist râles. The spinal fluid was clear, escaped under slightly increased pressure, and the Pandy reaction was positive. x-Ray examination of the chest revealed consolidation of a portion of the upper lobe of the right lung, which was interpreted as a probable carcinoma. Patient's symptoms were attributed to metastases. x-Ray on January 14, 1935, showed a small amount of osteo-arthritis of the dorsal spine. x-Ray on January 14, 1935, showed a destructive process involving the second and third thoracic vertebrae—characteristic of a metastatic malignancy—and there was beginning scoliosis. x-Ray of the head was negative. At that time patient developed inability to urinate, and frequent catheterizations were performed. Bronchoscopic examination revealed only redness in the right upper bronchus and there was no evidence of intra-abdominal new growth. No autopsy was made.

Case VII.—M. Z., fifty years of age, was admitted January 28, 1935. His complaints on admission were dyspnea, cough, frequent bloody expectoration and chest pain, of one and one-half months' duration. Patient was perfectly well up to one and one-half months previously when he had caught cold. He had a slight hemoptysis, increasing dyspnea, and a choking sensation over the upper sternal region. There was no loss of weight. Patient had a paroxysmal type of cough with occasional night-sweats. The previous history was negative except for a blow over the sternum during a robbery a year previous. Physical examination revealed an emphysematous chest with prominent dilated superficial veins over the left side. On percussion the left chest was flat throughout. The fingers showed marked clubbing and the lips and fingertips were markedly cyanotic. There was a small gland in the left supraclavicular fossa. On thoracentesis, 2400 cc. of sterile blood-tinged fluid was removed, which coagulated readily on standing. Bronchoscopy on February 1, 1935, revealed complete obstruction of the left main bronchus at the carina, and the bronchus was compressed to the opposite wall. The impression obtained was that of an extrabronchial pulmonary mass pressing on the bronchus. x-Ray examination at that time revealed a dense infiltration throughout the left lung with an area of encapsulated fluid in the upper third, and a dense increase of the right hilus markings. x-Ray examination revealed no apparent pathology

in esophagus, stomach, duodenum, or large intestine. The liver had become markedly enlarged. x-Ray on February 8th revealed collapse of left lung, with fluid level at the first interspace anteriorly. Microscopic examination of the excised gland revealed a metastatic squamous-cell carcinoma of lymph node with numerous mitotic figures. No autopsy was permitted.

Case VIII.—T. O., seventy-two years of age, was admitted March 9, 1935. Patient was in a different ward one year earlier where a diagnosis of tuberculosis was made following a pneumonia despite repeated negative sputa. The patient's complaint on admission was marked weakness, cough, and loss of weight. On physical examination, there was dullness, and flatness over the right upper lobe continuous from sternum into lung area. No râles were heard. Repeated sputa examination were persistently negative for the tubercle bacillus. x-Ray examination on March 27, 1935, revealed an infiltration of the right infraclavicular region which was called tuberculosis by the roentgenologist. During the patient's stay in the hospital at that time, he was constantly afebrile. x-Ray examination revealed a consolidation of the right upper lobe which was pronounced tuberculous. Our impression, however, as a result of the summation of the history and findings, was that this patient had a primary bronchus carcinoma. The autopsy revealed a hornifying squamous-cell carcinoma of a bronchus to the right upper pulmonary lobe, and a terminal pneumonia involving both right and left lower pulmonary lobes.

Case IX.—L. C., forty-eight years of age, was admitted August 22, 1935. He went home on release August 25, 1935. His complaints consisted of hoarseness, cough and severe pain over left side of chest, of six months' duration. He had lost considerable weight. No hemoptysis was present. Patient was afebrile. Morphine was needed to relieve pain. On physical examination, cyanosis was pronounced, the fingers and toes were markedly clubbed, and the chest was emphysematous. There was no expansion on the left side, and the interspaces were retracted. The right chest was hyperresonant, and the left chest was completely flat anteriorly and posteriorly. Patient went home in serious condition. Although this patient did not give us time for more thorough investigation, our impression was most decidedly in favor of a pulmonary carcinoma, and bearing in mind the possibility of error, we have decided to include this case, with some reservations.

Case X.—B. S., fifty-nine years of age, was admitted on September 17, 1935. His complaint was pain in the chest and cough of six weeks' duration. Patient was perfectly well up to six weeks before admission, when he began to notice knifelike pain in the right side of his chest which often radiated to the back, and which was aggravated by coughing or breathing. Cough was harsh and paroxysmal. There was slight hemoptysis. Dyspnea on exertion was very pronounced. There was a total absence of significant physical findings. x-Ray examination of the chest on September 21st revealed an opacity in the upper half of right side of chest, which was interpreted by the roentgenologist as an unresolved pneumonia, or as a tuberculous process. Subsequent x-ray showed a

partial consolidation with marked infiltration involving the upper lobe of the right lung. There was slight dulness on percussion. The infiltration showed a convexity downward. Repeated sputa examinations revealed no tubercle bacilli. The absence of physical findings, and the x-ray examination, spoke for malignancy. Bronchoscopic examination showed pus coming from the right upper and middle bronchi. There was no evidence of growth. Patient went home November 12th in poor condition.

The tabulation of this list of patients for one year from one medical ward permits the deduction of several important points:

First, the appreciation of the frequency of primary lung carcinoma.

Second, the frequency and the extensiveness and the widespread character of the metastases produce symptoms and signs in many parts of the body outside of the lungs. This is so frequently referred to as the protean manifestations of the disease and has led to the artificial subdivision into many clinical types depending upon the localization of these metastases, for example: cerebral, osseous, hepatic, gastro-intestinal, etc. This clinical subdivision may produce considerable confusion because it draws attention away from the primary lesion and particularly the pulmonary symptomatology. This clinical classification is not used in prostatic, breast, thyroid or kidney cancer metastases which produce somewhat similar focal metastatic evidence. It is better to recognize that the facility for systemic vascular dissemination exists in the lungs because of the contiguity of the primary growth to the rich vascular channels which may, and do, carry cancer cells to many distant organs and tissues.

Third, the local lesion and the pulmonary symptomatology, where a careful history is obtained, indicate pulmonary pathology in over 95 per cent of the cases.

Fourth, while many specialized examinations aid in the diagnosis, such as bronchoscopy, iodized oil injections, artificial pneumothorax, a strong presumptive diagnosis can be made on the history on the physical evidence, on the x-ray, and especially on the rapid progress of the lesion. Roentgenographic findings advance even in two to four weeks' time as illustrated by the first patient described. Such rapid changes are not usual in other conditions requiring diagnostic differentiation.

Fifth, biopsy examination of cervical or axillary lymph glands, bronchoscopic biopsy, the sputum, and pleural exudate, may reveal cancer tissue.

The clinical manifestations of primary lung carcinoma are protean in character. A simple clinical classification will include, first, those types in which the manifestations are entirely pulmonary in origin, and second, those in which the most prominent features are referable to metastases in nearby or distant areas, either with or without symptoms referable to the respiratory tract.

The onset of this condition is usually insidious. One never knows when the first seed of discord has planted itself in the bronchus. Many of the clinical manifestations may follow years after the occurrence of the original metaplastic bronchial changes. Once symptoms and findings appear, the patients may live from a week to as long as two or three years, the average time being one year. In one of our patients, a thorough physical examination revealed leg swelling due to saphenous varicosities, with no other findings present. Yet six months later, the condition presented itself as a far advanced carcinoma of the right lung with obstruction of the right main bronchus, terminating in death within one month.

Since bronchus carcinoma occurs frequently and is very menacing, one should have a definite method of diagnostic approach. In our clinic, the presence of any patient over forty, who has subacute or chronic complaints referable to the respiratory system of relatively recent origin, is sufficient to call our attention to bronchus carcinoma, and this possibility is kept in mind until a diagnosis is definitely made. Lung cancer is given the same differential diagnostic prominence that is accorded pulmonary tuberculosis. The history of freedom from previous respiratory distress becomes more important in diagnosis as age increases. An individual forty-five years old who develops a subacute or chronic respiratory disorder in the absence of previous history may equally well have tuberculosis, bronchiectasis, abscess, or neoplasm. A patient of fifty with the same story is more apt to have a neoplasm than a tuberculous process, and one of fifty-five or sixty, all things being equal, would most likely have a neoplasm. Chronic respiratory infections rarely precede the development of pulmonary

carcinoma. There may be short flurries of colds, influenza, or pneumonias preceding. These, however, are inconstant and not definitely characteristic.

Symptoms.—The symptomatology of pulmonary neoplasm may be identical with tuberculosis, abscess, and other chronic conditions. Fever is often present. Hemoptysis may be the first symptom to attract attention. It may be massive, or it may recur in small amounts from time to time. The sputum is often blood-streaked, "prune juicy" in character. In a massive lobar involvement, there may be a central necrosis. The abscess cavity thus formed may communicate with a bronchus, and yield a very fetid sputum.

Chest pain is a symptom, very frequently, of lung tumor. It occurs in upward of 60 per cent of the patients. The pain is described as stabbing, sometimes boring in character, and is due probably to marked irritation and tension of the parietal pleura, particularly in the hilar area. Where pain is present, the accumulation of large quantities of pleural fluid will not usually modify its character or intensity, while in tuberculosis, the pain is usually greatly relieved by the accumulation of pleural fluid.

Cough and dyspnea are often prominent symptoms especially in the rapidly progressing case where large bronchi are occluded or where there is an accompanying atelectasis with diaphragmatic paralysis. In a slowly progressing case there may be no dyspnea at all, or it may occur only as a terminal feature. Dyspnea may be due to large pleural effusions or copious bronchial secretions.

Cyanosis is frequently observed in association with large atelectatic areas. Cyanosis is also quite pronounced with the obstruction of the superior vena cava, a process that is sometimes rapid, but more often gradual in character.

Hoarseness, due most often to involvement of the left recurrent laryngeal nerve is sometimes present. Eye disturbances from sympathetic nerve involvement are not unusual. Dysphagia is often associated with encroachment upon the esophagus.

"Rheumatic pains" are often very pronounced with a carcinomatous involvement of the pleura, and they may even be the first manifestations of this important clinical condition.

The pains are often referred to the shafts of the long bones and may be so severe as to impede locomotion. Widening and spatulation of the fingertips and toes are often very apparent, especially with an associated long-standing bronchiectasis.

Cerebral symptoms, with single or multiple tumor nodules, or diffuse tumor involvement of the brain, are among the commonest sequelae of bronchiogenic carcinomata. The characteristic signs of brain tumor of pulmonary origin may appear even before respiratory symptoms are present, or before lung findings can be discerned by physical, bronchoscopic, or x-ray examination. The cerebral disturbances are sometimes of a purely mental character. Symptoms due to spinal cord involvement or metastatic changes in the vertebral column are frequently noted.

Marked weakness and anorexia are characteristic. Lowering of the blood pressure may be due to suprarenal involvement. The nourishment of these patients is sometimes fairly well maintained. The weight loss may be moderate or extreme.

Physical Examination.—The physical examination of patients with bronchus carcinoma will frequently reveal nothing. In fact, the condition is characterized by the paucity of findings in proportion to the extensive ravages of the disease, and to the extensive and pronounced x-ray evidence. Thus, in the presence of a central upper lobar involvement, there may be no findings whatever. Thus, in Case V, S. J. V., who had extensive findings referable to the central nervous system, an x-ray of the chest, made solely because of a suspicious area of dulness over the right apex anteriorly, revealed a lobar type of consolidation about as large as a medium-sized orange. No other physical findings were present.

The examination of the chest in lung cancer may reveal findings identical with those of tuberculosis, abscess or bronchiectasis. The difficulty in differentiation may be so great that, at times, even the x-ray will offer no help.

Neoplasms are very common in the right lung, particularly the right upper lobe being frequently involved, and we wish to draw attention to a physical finding not previously described which may be of benefit in recognizing this lesion. Although this sign is not typically pathognomonic of lung cancer, it is sufficiently characteristic, particularly in conjunction with the

history of onset previously described, to enable one to make an immediate tentative diagnosis of primary bronchus carcinoma with lung involvement after only a few moments of examination:

A collapsed right upper lobe will reveal absent breath sounds over a distinctly flat area. The heart sounds, especially the aortic second, can be heard loudly and clearly over this entire collapsed area anteriorly, extending from the sternum to the anterior axillary line. The sounds are frequently heard with equal intensity over the entire lobe area.

In Case X, there was a history of sudden onset with hemoptysis, and no previous history of lung involvement. Physical examination revealed absent breath sounds and flatness over the entire right lung, especially over the upper lobe. The loud aortic sounds were clearly heard over the entire upper lobe area. This immediately suggested a diagnosis of primary bronchus with massive pulmonary collapse, and retraction of the aorta to the right. *x*-Ray findings and the subsequent clinical course confirmed the diagnosis.

There is one other clinical finding of importance which has not previously been sufficiently stressed and which may be of assistance in differentiating tuberculous from neoplastic pulmonary tissue. In the presence of an extensive infiltration due to a tuberculous process, the breath sounds tend to the bronchial type and vocal resonance and vocal fremitus are most often increased. The reverse is true in neoplasms. Respiratory and vocal fremitus is usually poorly transmitted by carcinomatous lung tissue.

In addition to the characteristic onset, symptomatology, and findings as described, the *x*-ray is invaluable in recognizing the different clinical types, and in confirming the diagnosis. The fact that in a carcinomatous infiltration of the lung, the spread occurs with the convexity downward is especially significant. Fluoroscopy, also, is a valuable diagnostic adjunct, and often reveals diaphragmatic and mediastinal fixation. We call attention notably to the well-known fact that any extensive endobronchial involvement usually shows a corresponding atelectasis of that portion of the lung supplied by the occluded bronchus with some retraction of the mediastinal structure toward the affected side with the elevation of the diaphragm on

this side, although an enormous effusion will still produce displacement of heart to the opposite side.

Tumor cells, although rarely found in the sputum or in the pleural exudate, are of great importance in diagnosis. The persistent absence of tubercle bacilli from the sputum is significant. Bronchoscopic findings are important in every patient, but too much attention need not be given them. A careful perusal of our case reports indicates that negative bronchoscopic findings are neither incompatible nor inconsistent with a diagnosis of primary bronchus carcinoma. The first case tabulated indicates the danger of drawing conclusions from a negative biopsy report on tissue obtained through the bronchoscope. Our insistence upon a second bronchoscopic biopsy was rewarded by a positive diagnosis of carcinoma.

Summary and Conclusion.—The appreciation of the frequency of primary carcinoma of the lung is stressed so that early diagnosis will be suggested before metastases occur, thus permitting the prompt adoption of the radical complete surgical extirpation now being reported from many clinics.

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CLINIC OF DR. WALTER LINCOLN PALMER

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THE FUNCTIONAL BOWEL

WHEN invited to prepare a clinic on "The Functional Bowel," I was extremely reluctant to undertake the task because the subject is large and rather intangible. It is, however, as important as it is large and hence worth discussion.

The term "functional bowel" as applied to a disease is anomalous, for the normal bowel is "functional." Other terms such as "colitis" which are applied to the symptom-complex under consideration are perhaps equally inexact. Barger and others have pointed out that the etymological meaning of the word "colitis" is inflammation of the colon and that in the syndrome under discussion the colon is not inflamed in the sense that tissue injury is not demonstrable pathologically. If one accepts as a definition of inflammation "the response of tissue to injury," as Dr. George Dick has suggested, the term "colitis" is perhaps acceptable, for "cathartic colitis" and "mucous colitis" do seem to be instances of physiologic response to tissue injury although the histologic evidence of injury is questionable. The term "cathartic colitis" may be used in certain cases to emphasize the rôle of cathartics just as "mucous colitis" may be used to emphasize the amount of mucus present in the stool. An active bowel normally secretes mucus but in some cases the quantity is rather great and the mucus is retained in the contracted bowel, dried, and then expelled in short or long strings or shreds, the so-called "mucus casts" of the bowel, often containing considerable cellular detritus and stained with fecal material. The term "spastic colitis" was designed apparently to emphasize the element of spasm. In some cases the spasm in the sigmoid particularly does seem to be a prominent feature. In a sense, these terms are justifiable,

but on the whole it seems preferable to consider the phenomena as special manifestations of a more general disturbance of the bowel. The rather paradoxical term "chronic functional colitis" is sometimes applied. A more exact phrase would be "functional disturbance of the colon," but this seems too cumbersome for use.

Two other terms for the syndrome are commonly used in medical circles and are fairly exact, *i. e.*, "irritable colon" and "irritable bowel," implying merely an abnormal irritability of the colon. Still another term frequently used is that of "bowel distress," meaning distress arising from a structurally normal but functionally disturbed bowel, although by definition it should include any distress of bowel origin. It accurately describes the distress but it is not as satisfactory a name for the symptom-complex as "irritable colon."

The layman is perhaps more accustomed to the term "nervous indigestion" than to any other, and many physicians prefer the designation "gastric neurosis." This implies a psychoneurosis with predominantly gastric manifestations. It is true that many of the patients are psychoneurotics, but not all of them unless the diagnosis "psychoneurosis" is made with such a broad connotation as to include at some time or other the great majority of civilized mankind.

A more recent term is that of "abdominal migraine" which in its strictest sense is applied to abdominal manifestations seen in association with cephalic migraine—not the nausea and vomiting of severe migraine, but abdominal distress associated with migraine. When the term is applied to abdominal distress not associated with cephalalgia, its relationship to true migraine is obscure. In such cases "abdominal migraine" is synonymous with the various other terms described and equally inaccurate, for it implies an etiologic relationship as yet unproved.

Having thus criticized the term "functional bowel" and its various synonyms without finding any of them very satisfactory—"irritable colon," "bowel distress," and "functional disturbance of the colon" being perhaps the least objectionable—it is now appropriate to inquire into the nature of the syndrome under consideration. In the first place, it is important to recognize that it is not a disease entity, but rather a group of

symptoms resulting directly from a disturbance in the function of the bowel and indirectly from a host of causes.

Symptoms.—The most important symptom is abdominal pain, which may vary in severity from an indefinite sensation of bloating and distention to severe pain, usually cramplike, intermittent, rhythmical, lower abdominal, often related to and relieved by a bowel movement. The most familiar illustration of this type of pain is the "green-apple colic" of childhood. In adults, this type of pain, an intestinal colic, often simulates biliary or renal colic and the differential diagnosis may be difficult. The more chronic forms of "bowel distress" vary greatly in severity from patient to patient and in the same patient from time to time. The location of the distress also varies although it is usually lower abdominal and frequently shifts from point to point in the abdomen. It is frequently relieved by a bowel movement or the passage of flatus, although it may be brought on or made worse by a bowel movement. Food taking is likely to augment the distress just as eating or drinking is likely to cause defecation during an attack of acute enteritis due to intensification of the normal neuromuscular reflex. Many of the patients complain of continued abdominal soreness and discomfort not related to food taking or defecation. Nausea is a common symptom, particularly morning nausea (in men as well as in women!) and vomiting is not unusual. Abnormal or at least unusual hunger may be present consisting of "hunger pangs" referred to the mid- or lower abdomen and relieved by food taking. Belching, abdominal distention, rumbling and gurgling in the abdomen and excessive flatus are common. The patients often complain of more general symptoms such as headache, lethargy, fatigability, weakness, nervousness, insomnia, and dizziness but rarely if ever of true vertigo. These phenomena are of very questionable relationship to the "functional bowel" itself, but may be concomitant manifestations of a more general underlying disorder. It is possible, of course, that some of them may be reflex manifestations from the bowel.

Physical examination usually reveals a very tender palpable ropelike colon. The acute tenderness of an "irritable bowel" is really an amazing phenomenon in comparison with the lack of tenderness in severe chronic ulcerative colitis. Incidentally,

this localized bowel tenderness affords strong evidence that the pain is true visceral pain and not a peripheral sensory projection of a psychoneurosis, a so-called "psychalgia." The physical examination also gives the physician a clue as to the general sensitivity of the patient, the degree of "nervousness" present, and his or her reactions as an individual. Fever is absent, or at most, does not exceed 99° or $99\frac{1}{2}^{\circ}$ F. The leukocyte count is normal, although occasionally reports are received of 12,000 to 14,000. When checked, the count is usually found to be normal.

A detailed description of the bowel movements is very important. The patient usually refers to diarrhea, constipation, or "difficulty with the bowels" associated with the distress. Such statements cannot be taken at their face value for many patients consider themselves constipated if they do not have 3 "free" evacuations daily. Others are in the habit of taking a daily cathartic and of thus inducing one or two watery stools daily in order to keep their bowels "open" and because if they do not do so their bowels "never would move." It is important to find out exactly what, in terms of bowel function, the patient means by his statements. It is also very helpful to observe the stools from day to day or to have the patient keep a diary describing each stool in detail.

In analyzing bowel function it is necessary to bear in mind that the important consideration is the consistency of the bowel movement rather than its frequency. The chief functions of the colon are the absorption of water and the eventual evacuation of the undigested food residue. Diarrhea, therefore, is arbitrarily defined as the passage of stools softer than normal in consistency and constipation as the passage of stools harder than normal, the normal stool being considered as well formed, firm, and of good caliber. The vast majority of patients with "bowel distress" will describe some abnormality of bowel function when questioned. The exact nature of the disturbance whether diarrhea, constipation, or "spastic constipation" is of relatively less importance than the fact that it exists. In examining the stools of such patients it is important to observe the consistency, for the reasons mentioned, and also the form, for small caliber lead-pencil-sized or ribbon-like stools are frequently passed, due apparently to the spasm

present. Similarly, there may be an excess of mucus or "mucus casts." Cellular detritus may be found microscopically, but no frank pus or blood is seen unless local rectal lesions exist.

It is apparent, of course, that the symptomatology described may be present with organic disease in the bowel, elsewhere in the abdomen, or in some other part of the body. The physician's first task, therefore, is that of excluding organic disease by careful history taking, painstaking physical examination, thorough laboratory study including such x-ray examinations as may be indicated, and critical analysis of the patient's progress while under treatment. The experienced physician will be able to make the correct diagnosis eight or nine times out of ten on the basis of the history and the physical examination, but the pitfalls are numerous and best avoided by a thorough study and by eternal vigilance. If organic disease is disclosed, there may remain a valid question as to the extent the disease discovered is responsible for the symptoms. For instance, are the belching, distention, abdominal soreness, and stool disturbance to be attributed in a given case to the known cholelithiasis or not? And if these symptoms persist after cholecystectomy what then is the cause? These questions are very important for the syndrome is frequently seen in association with definite organic disease such as cholelithiasis, peptic ulcer, thyrotoxicosis, etc.

Assuming a patient with the symptomatology described, with a tender colon, definite stool disturbance, and no evidence of organic disease of any kind, what is the nature of the "functional bowel" disturbance? It consists apparently in an unusual or abnormal irritability of the neuromuscular mechanism of the bowel resulting in a disruption of the normal peristaltic rhythm. This may lead to hyperstalsis and diarrhea of varying grades or to spasm and "spastic constipation." The abnormal muscular contractions and the resulting localized distentions of the bowel produce distress which is true visceral pain, for muscular contraction and distention are known to be the two types of stimuli in the bowel capable of producing visceral pain.

The hyperirritability of the bowel apparently may come about in either one of two ways, or from a combination of the two. The first of these is the effect of irritants within the lumen of the bowel, such as results from the continued ingestion

of laxatives and irritating foods. The second is the nervous state of the individual. Some students of the subject are inclined to think a real "irritable bowel" never results from the first alone and that the disorder is always dependent upon a preexistent nervous condition. Their view is supported by the observation that the "functional bowel" is very rare in negroes and those individuals in our civilization who seem the least disturbed by the so-called "stress and strain" of civilized life. Be that as it may, it is clear that acute distress and stool disturbance may result from either one of the mechanisms mentioned, from "green-apple colic" or severe emotional stress, particularly fear, as is so well recognized in the lay literature of the world as a phenomenon of human experience (vide: Walter Alvarez, "Nervous Indigestion"; Erich Maria Remarque, "All Quiet on the Western Front"; "The Autobiography of Benvenuto Cellini"; H. Flanders Dunbar, "Emotions and Bodily Changes").

Treatment.—Adequate therapy depends primarily upon a correct diagnosis and upon a correct evaluation of the patient as an individual. This involves an appraisal of physical, social, and psychic factors. Dietary and pharmacologic therapy are likely to be valueless without a modicum of psychotherapy; psychotherapy alone may be sufficient to produce a cure, or, alone, it may fail. The most effective therapy as a rule is that which first gives due regard to the physical factors present; second, correctly estimates the social forces involved; third, provides adequate (usually rather superficial) psychotherapy; fourth, promotes bowel rest by a nonirritating diet; and fifth, promotes physical rest by enjoining a more satisfactory daily program, the use of sedatives, and the attainment of peace of mind. The failures are those cases in which the patient does not cooperate or in which the program cannot be carried out completely because of external factors. Continued distress and difficulty in a cooperative patient are very often due to an unsolved psychiatric problem or an impossible "life situation."

Probably the one most important therapeutic item is physical and mental rest. Shakespeare was well aware of the importance of sleep, "balm of hurt minds," "sore labor's rest," "chief nourisher in life's feast." It is well to suggest definite and longer hours of sleep and to give sedatives if necessary to

assure it. An afternoon rest is very helpful. In many cases a few days, in some even a few weeks of absolute bed rest is desirable in order that the patient may become thoroughly rested. The application of heat to the abdomen in the form of a hot-water bottle or an electric warming pad often gives great relief. Tincture of belladonna in doses of 40 to 45 drops daily is of value.

Cathartics should be avoided. Even mineral oil by mouth is unnecessary and serves to perpetuate the patient's notion that he must take something in order to make his "bowels move." Adequate bowel function can be restored by dietary means aided from time to time if necessary by oil or small water enemas or glycerin suppositories. These are to be used not to aid the stool in getting through the colon into the rectum, but only if the patient is unable to expel the stool from the rectum properly. This should be determined by digital examination. An oil retention enema of 3 or 4 ounces of mineral oil may be given on retiring if the stool on a given day has been very hard and dry and it is feared that the passage of another such stool may bruise the anal orifice. In the first few days fecal impactions may occur, and the physician must be alert to detect their presence. Soft fecal impactions are often as difficult to evacuate as hard ones and require repeated enemas and rectal examinations.

The principle of dietary management is that of attempting to find a diet containing the proper amount of laxative material for each patient. It should be sufficiently laxative to produce firm, formed stools rather than hard ones and not sufficiently laxative to produce soft stools. Incidentally, it may be noted that hard stools in the presence of marked abdominal distress usually signify spasm and too much irritation rather than too little.

In the following diet list¹ the first paragraph of section I is used as a basic diet. As the patient improves, oatmeal and potato are added and gradually further stipulated and strictly

¹ The general scheme of this diet as well as the treatment of the entire subject is based on the work and usage of the late Dr. B. W. Sippy and his associates to whom I desire to give full credit without assigning to them responsibility for any deviations that may have crept into my thought and practice in the past fourteen years.

limited additions from sections II and III may be made. On the whole the sections and the subdivisions are arranged in the order of a gradually increasing laxative effect, section II being more laxative than section I, etc., and subdivision 2 being more laxative than subdivision 1. There are exceptions, however; ripe banana, for instance, is often tolerated better than apple sauce or rhubarb. The quantitative factor must be also considered as well as the qualitative.

I. *Foods with Very Little Mechanical or Chemical Irritant* (low residue, non-laxative):

1. Lean meats of all kinds, cooked eggs, milk and cream, cream of wheat, rice, white bread, butter, crackers, cheese, farina, noodles and spaghetti without tomato and peppers or such seasoning, custard, jellies, cornstarch and tapioca (no Krumbles or bran flakes).
2. Oatmeal, whole wheat bread and baked or mashed potatoes.

II. *Cooked Vegetables with Large Amounts of Mechanical Irritant but with Relatively Small Amount of Chemical Irritant:*

1. Spinach, asparagus, carrots, celery, sweet potato, peas.
2. Beets, string beans, tomatoes, turnips, parsnips, squash, brussels sprouts.
3. Cauliflower, corn, onions, sauerkraut, cabbage.

III. *Stewed Fruits* (slightly more laxative than the vegetables):

1. Stewed prunes, stewed peaches (least laxative).
2. Apricots, pears, berries of all kinds, cherries, grapes, stewed apples, apple sauce, baked apples, rhubarb.
3. Figs, raisins, dates.
4. Jellies, jams, and marmalades.

IV. *Raw Vegetables* (on the whole more laxative than the cooked):

1. Celery, lettuce, tomato, onion, cucumber, cabbage, radishes.

V. *Raw Fruits* (on the whole more laxative than the cooked):

1. Oranges, bananas, grapefruit (least laxative).
2. Peaches, pears, apricots, apples, berries, cherries, grapes, melons, plums.

VI. *Miscellaneous Foods Which Are Very Laxative* (eat cautiously, if at all):

1. Nuts, ice-cold drinks of all kinds, buttermilk, fruit juices.
2. Bran, honey, syrup, molasses, candies.
3. Beer is very laxative.
4. Ice cream is laxative for some people.

The majority of patients find it necessary to continue some dietary restriction more or less indefinitely in order to live comfortably. It will be noted that this program forms a basis for

the treatment of both diarrhea and constipation—conditions not to be differentiated as sharply as prevailing notions among the laity and many physicians might indicate.

Allergists in reading this article, if any do, will undoubtedly feel that the factor of specific food sensitization has been ignored. There can be no doubt that certain food sensitizations do occur and that nausea, vomiting, abdominal pain, and diarrhea may be the result of the irritating effect of such foods on the gastro-intestinal tract in these sensitized individuals. In my experience, however, such manifestations have invariably been the acute phenomena mentioned: nausea, vomiting, cramps, and diarrhea. My associates working in the field of allergy have studied the problem from their point of view and have arrived at the same conclusion. This calls into question the mechanism of action of the so-called "elimination diets." Some of them may be effective, independent of any allergic factor, in that they lead to the elimination of the more laxative foods. The psychotherapeutic value of the "elimination diet" is also not negligible.

Psychiatrists in reading this article, if any do, will feel that insufficient attention is paid to the psyche, both etiologically and therapeutically. From the standpoint of etiology they may be right; from the standpoint of therapy, I doubt if they are. The procedure and method of approach outlined is effective in the vast majority of patients although it is superficial from a psychiatric point of view. In many cases detailed psychiatric study is absolutely necessary, and in many it effects a cure not possible by any other procedure. But detailed psychiatric study, including psychoanalysis, must be reserved for the more difficult cases because it is time-consuming and costly for both patient and physician and because, all too frequently, in these difficult cases, the "life situation" of the patient is so impossible that a satisfactory solution cannot be found. The patient must then be aided by the physician in the struggle to carry on and through. Some of these unfortunate individuals exhaust the patience of a saint, be he psychiatrist, internist, or general physician, but others exhibit the most amazing feats of courage and fortitude, gaining control of themselves if not of "the situation."

Two cases will be described in some detail as illustrative,

although I have purposely chosen two in which the emotional elements are prominent, in order to emphasize the important contribution a skilled social worker may make in the handling of the problems encountered.

Case I.—The first case is that of a twenty-six-year-old Italian factory girl who entered the clinic complaining of nausea, particularly in the morning before breakfast, of three months' duration, anorexia and belching of eighteen months' duration, and burning in the epigastrium of three months' duration. A typical day was described as follows:

- 6.30 A. M. Awakens with nausea and an ache in the stomach.
- 7.00 Breakfast: oatmeal and 1 glass of hot milk. No relief from distress. Nausea and burning one-half to one hour after breakfast.
- 9.15 Recess. Drinks pint of milk, eats a sandwich, and obtains relief.
- 12.00 Distress returns, but not as severe as earlier. Takes fruit and water.
- 5.00 Distress has been present since noon although mild in character. Patient eats dinner and is hungry. Omits meat if she feels badly. Eats vegetables and potato and 1 glass of milk.
- 8.00–9.00 P. M. Distress—fiery burning in epigastrium and lump at the lower end of esophagus.
- 10.00 Drinks another glass of milk before she goes to bed but does not get to sleep until 12.00 because of restlessness and distress. Sleeps soundly, never awakened by pain during the night.

The bowel function was described with the phrase "not so good," by which she meant they moved only once every two or three days. The remainder of the history was not important. The physical examination was normal except for tenderness along the ascending colon. The blood Wassermann and Kahn tests, blood counts, urinalysis, gastric analysis, stool analysis (including search for parasites) and x-ray examination of the gallbladder and stomach, were all normal. The patient was reassured with regard to the absence of organic disease and given the basic diet outlined above with the stipulated addition of 2 dishes each per day of cooked vegetables and cooked fruits. Tincture of belladonna was prescribed. Two weeks later the patient reported marked improvement, freedom from distress, and one well-formed bowel movement daily. Six weeks later she complained of a choking sensation in the throat and chest. The bowels were then moving twice a day but the stools were well formed. The cooked vegetable and fruit were reduced to 1 each daily; 1½ grains of phenobarbital was prescribed to be taken at bedtime.

A detailed study of the social aspects of the case was then made by Miss Georgia Ball of the Department of Social Service, who has condensed the results of several hours spent with the patient in 4 conferences over a period of two months in the following summary:

"The Social study disclosed an intelligent 26-year-old Italian factory worker who suffered an intense emotional strain as the result of hard, nerve racking work, personal deprivation, heavy financial responsibilities, and many family worries. Her life was devoid of any interest other than her symptoms afforded. Her father had died when the patient was fourteen years of age. She then

became the support of her invalid mother and young brothers and has retained responsibility for them. Three years ago, seniority in the factory imposed on her increasing responsibility until she was in charge of nineteen machines and five workers, with very little additional pay. At this time, the ill health of a brother caused the patient more worry and great financial pressure. She first noticed abdominal pain after eating certain foods during this period of excessive strain. She became somewhat accustomed to her nerve racking work, and the family responsibilities lessened somewhat, but her life had become monotonous and barren.

"The relationship between the social situation and the physical symptoms was discussed with the patient. She did not wish to make a vocational change, and hence an attempt was made to educate her to the necessity for interests outside of her work. She responded eagerly, and made use of the discussions regarding a change in her mode of life. The symptoms disappeared, with the exception of a recurrence of abdominal distress when she was placed in charge of two departments in the factory. She was aware that the additional responsibility was an important factor in the recurrence of symptoms and demanded release from the added work. The symptoms disappeared, according to the patient's statements, when her employer complied with her demand. She took advantage of opportunities to go bowling and swimming, went to a girl's club and a church party. She expressed concern with her lack of mental growth, asked for and was given guidance in a planned course of reading."

The patient has remained symptom-free for the past eight months and has grown increasingly happy, cheerful and filled with zest for life, as though emancipated from bondage. Legitimate questions may arise with regard to the relative importance of the various therapeutic procedures, diet, medication, reassurance, the kindly and helpful interest of Miss Ball, the patient's awakened interest in outside activities, etc., but there can be no question as to the total therapeutic effect.

Case II.—The second case is that of a twenty-five-year-old married woman who came to the clinic with the following complaints: loss of 20 pounds of weight and vomiting after breakfast for six months; diarrhea (7 to 8 loose movements daily), cold hands, headaches of indefinite duration, and abdominal pain beginning in the upper abdomen and traveling down both sides to the inner aspects of the thighs, for one year. The detailed analysis of the symptoms, the system inquiry, and the physical examination may be omitted, except for the statement that the colon was palpable and rather tender and that at the time of the first examination, the patient was obviously very much disturbed emotionally. A proctoscopic examination was normal. The blood Wassermann and Kahn tests were normal as was the blood count and the urinalysis. Repeated stool examinations were negative for occult blood by the benzedine test. The basal metabolic rate was 5 per cent. No x-ray studies were made. The patient was reassured and given a low residue, nonlaxative diet (section I of tabulation) without fruit or vegetable. Medication consisted at first of sodium bromide and phenobarbital and tincture of belladonna. Within a month the stools became formed, 1 or 2 per day. During the succeed-

ing seven months there was gradual improvement and a 16-pound gain in weight. At the present time there is very little distress and no diarrhea, the stools being formed, one or two daily. The patient is still on the original diet without fruit or vegetables, but with liberal quantities of raw milk. There have been occasional recurrences of diarrhea and distress almost invariably resulting apparently from emotional difficulties, over which the patient has slowly gained partial control.

Miss Ball's summary of many hours of work in 15 or 16 conferences with the patient, both in the clinic and in the patient's home, is very illuminating.

"In the first interview the patient wept as she told of a plight she considered intolerable and unalterable. She had married two years previously a man with five young children, and although she loved her husband, she found the burden of the housework and care of the children more than she could manage. The most aggravating factor was the presence of the 14-year-old stepson whom the patient could not discipline and who did everything he could to annoy her. Further study revealed that at the time of her marriage the patient had created a large debt by the purchase of fine furniture, and that its care and preservation had become paramount in her life in order to justify the financial obligation she had imposed upon her husband. She exhausted herself in the immaculate care of the large house and the furniture and had neither vitality nor reserve to cope with the stepson's resentment of her usurpation of his place with his father. The household grind and lack of social activities accentuated her loss of perspective.

"Social treatment over a six months' period has included the provision of a period of complete rest for the patient in a convalescent home and of a W. P. A. housekeeper to assist with the work. Education of the patient and her husband has been attempted in relation to the cause of the boy's behavior and methods by which it may be treated. An increase in their understanding and an improvement in the patient's attitude can be observed. The problem is not yet solved, but the patient's nervousness has decreased; she is no longer hysterical and irritable, she has attained greater satisfaction in living as the result of the adjustment of the household routines, the lightening of her duties by the housekeeper, and the development of some social life, she has gained weight, sleeps well, and her physical condition is greatly improved."

Here again it is difficult to decide whether the credit for the definite improvement is to be given to the conscious or unconscious psychotherapy, to the diet, to the medication, to the additional rest afforded by the W. P. A. housekeeper, or to the patient's greater interest in activities outside of her home and her greater opportunity to engage in them. It seems more rational to consider the effect the resultant of all of these various factors.

Conclusions.—Terminology is, after all, of very little significance. The important point is the recognition of the broad aspects of the varied symptomatology of "the functional bowel" and an approach designed to determine, first, whether or not organic disease exists; second, the significance of the disease in

relation to the life of the individual; third, the determination or evaluation of the various factors involved in the functional disturbance in the case under consideration, and finally, the planning of an intelligent program of rest, exercise, diet, medication, and mental hygiene in order to bring about a more satisfactory adjustment between the individual and the environment, both internal and external.

CLINIC OF DR. STANLEY GIBSON

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GASTRO-INTESTINAL PATHOLOGY IN INFANCY

It is my purpose in the present discussion to consider a few gastro-intestinal conditions in infancy in which prompt diagnosis and proper treatment are highly important.

Case I. Hypertrophic Stenosis of the Pylorus.—R. N., a first-born male infant was brought to the clinic at the age of four weeks. He weighed 6 pounds 4 ounces at birth, was breast fed, and had gained satisfactorily. Three days before coming to the hospital, he had vomited twice. On the following day he vomited three times, each time shortly after nursing. The next day the vomiting was even more marked, and the mother was convinced that he had kept practically none of his feeding. He also vomited water which had been offered between the breast feedings. The vomiting occurred during or shortly after feeding and was forcible in character. Squirring and crying sometimes preceded the vomiting. The bowel movements had become smaller and less frequent since the onset of the vomiting. The baby had lost 4 ounces in weight.

Physical examination revealed a well-developed and well-nourished baby of good color and fair tissue turgor. When he was observed as he lay quietly, inspection of the upper abdomen showed no abnormality. After nursing for a few minutes, he was again examined, and it was now noticed that the entire stomach area seemed more prominent than normal. Then in a short time a rounded elevation comparable in size to a golf ball was noted in the region of the cardiac end of the stomach. This prominence progressed from left to right to disappear at the pyloric region. Peristaltic waves followed each other in close succession so that 2 or 3 elevations could be seen at one time. Palpation at the outer margin of the right rectus muscle slightly above the level of the umbilicus revealed a small hard mass which was freely movable.

The history and the physical findings were pathognomonic of hypertrophic stenosis of the pylorus, and operation was performed without delay. The circular muscle fibers were incised down to the submucosa according to the Fredet-Ramstedt technic.

In the above cited typical case in which the onset was sudden, the diagnosis clear, and the child was in good condition,

preoperative care was relatively unimportant. In the late neglected case in which dehydration is marked, improvement of the patient's condition prior to operation is most important. Ringer's solution subcutaneously, Ringer's solution and glucose intravenously, or blood transfusion, depending upon the indications in the individual case, should be given.

A word concerning the operation itself may not be out of place. It is important that the circular muscle fibers be incised throughout the entire length of the pylorus, otherwise the obstruction is not relieved. I have seen several cases in which a second operation was necessary.

Postoperative care consists chiefly in supplying nourishment as rapidly as the baby's tolerance will permit. Breast milk should be used if it is obtainable. Otherwise boiled cow's milk or evaporated milk in proper dilution may be employed. Feedings should be frequent and small in amount at first, 1 or 2 drachms every two hours with an equal amount of water or 5 per cent glucose solution midway between the milk feedings. If there is no vomiting the feedings may be gradually increased in amount and the intervals lengthened so that at the end of about three days the full food requirement for the baby's age and weight may be given.

The pathogenesis of hypertrophic pyloric stenosis is imperfectly understood. That a combination of pyloric hypertrophy and pylorospasm is responsible for the symptoms is generally conceded. It is difficult to believe, in view of the great thickening of the pyloric musculature frequently observed at operation, that so great a hypertrophy could occur within the short space of time during which symptoms have been present. This would suggest that the hypertrophy antedates the onset of symptoms and is probably congenital in nature. Yet if this were true one would expect to find hypertrophy of the pylorus not infrequently in necropsies on new-born babies. So far as I know, such findings have not been reported.

Case II. Pylorospasm.—M. K., a female infant, was first seen at the age of six weeks. The chief complaints were that the baby cried a great deal, especially after feedings, vomited frequently, and was not gaining satisfactorily. The baby was artificially fed, receiving a formula suitable to its weight. The mother stated that the vomiting occurred sometimes before the feeding had been finished, sometimes shortly after feeding, and sometimes an hour or more

after feeding time. The vomiting was often preceded by evident discomfort, and varied in amount from a few teaspoonfuls to what appeared to be the entire feeding. The vomiting was usually rather forceful in character. The stools were normal in number and consistency.

Routine physical examination was negative. A feeding was given and the baby's abdomen observed during this period. After most of the feeding had been taken, the baby began to squirm and whimper. The outline of the stomach could be made out standing prominently above the level of the remainder of the abdomen. As one continued to observe the stomach outline, indefinite contractures could be seen suggesting gastric waves, though there was no continued progression from left to right. Palpation failed to detect a pyloric tumor.

The symptoms of vomiting, forceful in character, the discomfort before vomiting occurred, the unsatisfactory gain in weight, and the absence of clear-cut gastric waves and palpable tumor suggested the presence of pylorospasm.

A concentrated formula was given, consisting of equal parts of evaporated milk and water with addition of a dextrimaltose preparation. The baby's weight was 8 pounds. The formula prescribed was 8 ounces of evaporated milk, 8 ounces of water, and 3 level tablespoonfuls of dextrimaltose, 5 feedings daily. In addition to the concentrated feeding atropine sulfate, $\frac{1}{1000}$ grain, was administered by mouth fifteen minutes before each feeding. On this régime the baby became more comfortable, vomiting became infrequent, and an adequate gain in weight occurred. As the baby improved, the dosage of atropine was diminished, and the feedings were increased in volume by addition of more water to the formula. By the end of the third month all evidences of pylorospasm had disappeared.

Although this patient responded promptly to the simple therapy outlined above, results are not always so readily obtained. The more difficult cases will often test the skill and patience of the experienced physician.

As previously mentioned, the giving of small concentrated feedings decreases the likelihood of vomiting. When vomiting does occur, refeeding should be attempted and is often taken well and retained. It is a curious fact that minor changes in the character of the food may often materially lessen the amount of vomiting. Thus the utilization of boiled cow's milk, evaporated milk, sour milk mixtures, etc., the formula being changed every few days, may be of distinct benefit. In the severer cases stomach lavage preceding the feedings is indicated.

Thickening the feeding with farina or other cereal is often successful where concentrated feeding alone fails to relieve the vomiting. The hole in the nipple must be large enough to

allow easy passage of the thickened mixture, or resort to feeding from a spoon or spatula may be employed. When the total fluid intake is insufficient for the baby's needs, parenteral administration of fluid is necessary.

Atropine has been the drug most widely used in the control of pylorospasm. The individual tolerance varies within wide limits. A sufficient amount should be given to produce some flushing and dilatation of the pupils. It should not be forgotten that overdosage may produce a fever up to 104° F. or even higher, also that the baby may acquire an intolerance to atropine which in itself is a cause of vomiting.

Phenobarbital has been found of value, especially when atropine is not well tolerated. A dosage of $\frac{1}{8}$ to $\frac{1}{4}$ grain before each feeding is the amount usually recommended. It has been my custom frequently to combine atropine and phenobarbital, and the results have seemed more satisfactory than with either drug alone.

Finally roentgen ray treatment of the thymus has been found to control the vomiting in a certain percentage of cases.

The 2 typical cases presented above furnished no difficulty in diagnosis. It not infrequently occurs, however, that the differential diagnosis between actual hypertrophy of the pylorus and pylorospasm may be difficult. The weight curve is an important differential point. Weight gain may be slow and irregular in pylorospasm. In stenosis there is usually a distinct, and sometimes rapid loss in weight. A second point is the character of the stools. They are usually normal in pylorospasm, whereas they are infrequent and scanty, often an actual starvation stool, in stenosis. In doubtful cases, administration of barium, followed by x-ray examination, to determine gastric retention is helpful. The important point to remember is that medical treatment should not be continued if the baby is losing ground. Under such circumstances operation is safer than delay.

Case III. Intussusception.—At 10 o'clock one night, a mother called on the phone, asking that I come immediately to see her five months' old baby girl. She said, "I am sure she is going to have a convulsion. She acts just as my older girl did before she went into a convulsion. She cried very sharply, turned pale, and drew up her arms and legs as if in great pain." She then added that she had just finished giving the baby an enema, and that a little

blood had appeared with the bowel movement. The baby was breast fed, and had been in perfect health until the sudden attack described above.

A few moments later I arrived at the home. The baby was still lying on the side of the kitchen sink where the enema had been given. As the baby lay there, she presented an interesting study. The striking feature seemed to be that she was wholly uninterested in her surroundings. She was staring into space, paying no attention either to the mother or to me as we moved about her. There was also a pinched expression, and the face was distinctly pale. After a few moments the baby seemed again to be in extreme pain, cried sharply, and drew up the arms and legs. These spasms of pain recurred at frequent intervals. When the crying had ceased, the baby again assumed the abstracted far-away stare.

The routine regional examination was essentially negative. The temperature was normal. There were no abnormal reflexes. Palpation of the abdomen failed to reveal any rigidity or the presence of a tumor mass. Rectal examination was also negative. Shortly after the physical examination, the baby vomited. The baby was then observed for half an hour during which time several spasms of pain occurred. At the end of this time, another enema was given, and a small amount of blood-stained mucus with little fecal material was obtained. Reexamination of the abdomen was again negative. A half hour later, however, a distinct sausage-shaped mass could be felt extending transversely in the upper abdomen, best palpated in the midline. This finding practically clinched the diagnosis of intussusception. However, another rectal examination was made at this time, still with negative results. No tumor could be felt in the rectum, and no blood appeared following withdrawal of the examining finger.

The baby was taken to the hospital, and surgical consultation obtained. The surgeon did a rectal examination with negative results. It also happened that the tumor mass which I had previously felt between the rectimuscles in the upper abdomen, had shifted in position so that it was not readily palpated. I could sense that the surgeon was not convinced of the diagnosis and asked him whether he would like the baby to have another enema. At this juncture the mother said, "I felt that tumor myself while I was waiting for the arrival of the surgeon. I know that there is something radically wrong with the baby. If an operation is necessary to cure her, let's get it over with right away." Whereupon the operation was performed at 2 A. M., four hours after the first symptom. An ileocecal intussusception was found, which had progressed for a distance of only about 2 inches. Recovery was prompt and the baby returned home at the end of four days.

The above case of intussusception is interesting from a number of standpoints. In the first place the mother called immediately after the onset of symptoms so that opportunity was furnished to observe the evolution of the cardinal findings. It was interesting that within a few moments after the onset, when the first enema was given, bloody mucus was seen in the

stool. It was also interesting and most unusual to fail to obtain a gush, or even an ooze of blood-tinged mucus following the withdrawal of the finger from the rectum. This was probably due to the fact that the intussusception had progressed only a short way, and insufficient bloody serum had been squeezed from the intussuscepted bowel to appear at the rectum. In other respects the symptoms and signs were characteristic of intussusception.

Because of the relative frequency of intussusception in infancy, and because prompt surgical relief is a life-saving measure, the importance of early diagnosis cannot be overestimated.

The onset is usually characteristic. A baby, usually in good health, is seized with a sudden attack of what appears to be a severe colic. The baby cries out, draws up his legs and arms, and has an expression of pain in his face. The attack passes quickly, to return at intervals of half hour or less. In the intervals between attacks, the baby's expression is that of mild shock, the face being pale, and the gaze directed into the distance. The baby has little interest in his surroundings, and does not object to the physical examination, even the examination of the rectum.

The appearance of blood in the stools of an infant should always arouse the suspicion of intussusception, and it is well to regard the diagnosis positive until it can be ruled out. At first the blood is mixed with fecal material, but after the lower bowel has been emptied, blood-tinged mucus resembling currant jelly is passed. Digital examination of the rectum is essential. In the first place one may in some instances be able to palpate the apex of the intussusception if it has extended as far as the rectum. Still more important is the fact that when the examining finger is withdrawn from the rectum, the escape of jelly-like mucus described above is practically diagnostic of intussusception. This finding may be present hours before blood is spontaneously expelled from the rectum.

The palpation of an abdominal mass is usually possible though failure to feel a tumor does not exclude intussusception. In my experience the mass is more often felt in the midline or to the left rather than in the ileocecal region itself.

If one has in mind the possibility of intussusception the

diagnosis is not apt to be missed. The chief conditions to be considered in differential diagnosis are those in which blood may be present in the stools. Acute gastro-enteritis may produce bloody stools but there is fecal material along with the blood. Furthermore, diarrhea is usually present for some time before the passage of blood. There is no tumor. A bleeding Meckel's diverticulum may be responsible for bloody stools, but here again the blood is mixed with the bowel movement, acute colic and shock are usually absent, and no tumor is felt. Henoch's purpura may be responsible for blood in the stools, but in this condition there are usually hemorrhagic spots over the body, and the other cardinal signs of intussusception are lacking.

The outlook in cases of intussusception depends almost wholly upon the length of time which elapses before adequate surgical interference is instituted. It is true that a very small percentage do reduce spontaneously, but this outcome is not to be expected. Operation within the first twelve or twenty-four hours yields almost uniformly good results. Operation at a later time may be unsuccessful, due either to extensive damage to the intussuscepted bowel, or to absorption of toxic products from the small bowel above the point of obstruction.

Other methods of treatment, such as rectal injections of barium with observation under the fluoroscope, are too uncertain in their results to be given serious consideration. One cannot be certain that the obstruction is completely relieved, and in the meantime valuable time is being lost. Prompt diagnosis and immediate surgery are the means of lowering mortality in this not uncommon condition.

Case IV. Meckel's Diverticulum.—F. M., a male infant, was brought to the hospital at the age of nine months. There had been intermittent bleeding from the rectum during the past three months. On a number of occasions blood clots had been observed. The baby had shown no signs of abdominal distress. Between 7 P. M. and 3 A. M., of the day of admission, the patient had expelled about 3 teaspoonfuls of blood. Some of the blood was dark, some of it was red, and there were numerous clots. The baby seemed to be uncomfortable. The mother stated that the baby's face was "paper white" during the time that the passage of blood had occurred. The baby had been well except for the ailment described above.

Physical examination revealed a well-nourished infant who was rather pale. He was alert, and apparently free from pain. The abdomen was soft.

No mass could be felt. Rectal examination was likewise negative, save that on withdrawal of the examining finger, some dark, clotted blood oozed out.

Rectal temperature on admission was 100° F. Red cells numbered 2,970,000, white cells 17,500, hemoglobin 55 per cent.

Inasmuch as the baby seemed comfortable and there was no evidence of further bleeding it was thought best to observe the baby for a brief period, and in the meantime arrange for blood transfusion should the occasion arise.

The diagnosis in this case concerned itself with intermittent hemorrhage of three months' duration somewhere in the gastro-intestinal tract. The fact that some of the blood was dark and clotted, and some was relatively fresh would suggest that the hemorrhage was neither high up in the small bowel nor near the rectum, but at some intermediate point. This reasoning would apply only on the assumption that all of the bleeding had come from a single focus. In discussing the previous case, I stated that in every instance where blood appears in the stools, it is necessary to consider the possibility of intussusception. In this case intussusception could be excluded by the fact that symptoms had been present for months, there had been no vomiting or severe colicky spells, and no abdominal tumor.

Rectal polyp or adenoma had to be considered, and the rectum was explored by means of the proctoscope with negative results.

The history and the physical findings were suggestive of a bleeding Meckel's diverticulum. After a day of observation in the hospital, operation was performed. During the operation 150 cc. of blood and 300 cc. of saline were given intravenously. About 10 inches above the cecum a Meckel's diverticulum, the size of the tip of one's thumb, was found. A few fibrous adhesions were present around it. The diverticulum was removed. The baby made an uneventful recovery.

The pathologic examination of the diverticulum revealed the presence of gastric mucosa, and an area of ulceration which accounted for the hemorrhage.

The above case illustrates a type of accident that occurs not infrequently in Meckel's diverticulum. It may also produce other types of pathology. Meckel's diverticulum may be the starting point of an intussusception. It may rupture with a rapidly spreading peritonitis. It may adhere to surrounding structures and cause intestinal obstruction. It may become acutely inflamed, simulating acute appendicitis. These possibilities remind us that Meckel's diverticulum must be kept in mind in any consideration of abdominal pathology.

I have purposely limited my discussion this morning to types of gastro-intestinal lesions which present a fairly clean-cut clinical picture, which may be diagnosed readily if they are kept in mind, which yield to prompt treatment, and which if not treated promptly and effectively may result in tragedy.

CLINIC OF DRS. JULIUS H. HESS AND RALPH H. KUNSTADTER

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DIAGNOSIS AND TREATMENT OF OBESITY IN CHILDREN

OBESITY signifies an abnormal increase of fat in the subcutaneous connective tissue. The term does not imply a clinical entity or syndrome, but merely an abnormal symptom or sign, the etiology of which must be determined if proper and adequate treatment is to be prescribed.

It is impossible to state when normal fat deposition stops and excessive storage begins. Many mathematical formulae have been devised to calculate the expected body weight from the stature. However, from a practical standpoint it is more satisfactory to resort to tables such as those of Faber, Baldwin and Wood and others, determined on the basis of normal averages for age, height and weight. Usually a child is considered as obese when the excess surpasses 20 per cent of the average normal. All of the mathematical methods in present use for determining the extent of obesity are open to criticism. Individual variations in body build and in constitutional distribution of fat must be given consideration. In other words, a child may not be greatly overweight according to accepted standards of measurements and yet, on inspection of the child, it is observed that fat is not uniformly distributed but has accumulated abnormally in certain regions of the body, the significance of which is far more important than the degree of overweight. Thus, obesity must be viewed as a medical problem and not simply as a matter of overeating.

In a general way, obesity is considered to be one of two types: *exogenous* or *endogenous*. In the former, it is due to

a disproportion between the food ingested and the food required for body maintenance, energy and muscular exercise—sometimes spoken of as hyperalimentation—the adiposity being uniformly distributed, although more pronounced in the normal fatty regions, viz., chest, hips, buttocks and thighs. However, strictly speaking, obesity due to hyperalimentation *per se* is the exception rather than the rule. Gordon¹ in a recent study of obesity in children, states that in his experience overeating *per se* is an infrequent cause of obesity in children and that when there is overeating it may be because of factors either endogenous, exogenous or both. Barr² asserts that clinical and laboratory experience has demonstrated that, although such factors as lack of exercise and excessive consumption of food are of great importance in the production of adiposity, they are not alone sufficient to permit a great fat accumulation in many individuals. It is our feeling, also, that the majority of children are not abnormally overweight because of excessive eating alone, but because there are endogenous factors present that account for a disturbed metabolism; these may also cause an excessive appetite.

Endogenous obesity, the type about which we are most concerned, signifies abnormal body metabolism. Various factors may modify the normal chemical and physiologic processes of the body. These factors include heredity, constitution, the nervous system and the endocrine glands. It is the close interrelationship of all of these factors and our meager knowledge of the part played by each that adds to the confusion covering the pathogenesis of obesity.

The hereditary nature of obesity cannot be overlooked. In fact, Beardwood³ designates heredity as the most important single factor. Dunlap and Lyons⁴ traced a history of obesity in the parents of 69.2 per cent of the 523 cases they studied and Van Noorden⁵ states that 80 per cent of all cases of obesity are familial. Bauer⁶ reports a familial incidence of 88 per cent. Nixon⁷ has well stated that there must be some inherent tendency: constitutional, metabolic, endocrine, or neural in origin, which must be offered in explanation of why children of the same family, living in the same environment, and eating the same food will differ in the fat regulating mechanism.

In the constitutionally obese there is a decrease in the specific dynamic action of the proteins and the carbohydrates to stimulate metabolism.⁸

Juvenile obesity not infrequently follows infectious diseases in childhood. Whether it is a result of the prolonged inactivity due to the illness or some toxic effect upon the endocrine system is difficult to say.

It is our purpose with the limited knowledge that we possess of the interrelationship of the endocrine glands in obesity, to emphasize that many of our children with obesity have as a background a defective endocrine system and in this presentation we shall attempt to classify our cases of obesity according to what we believe to be the most significant endocrine glands involved, both from a clinical and laboratory standpoint.

Excluding simple hyperalimentary overweight, the majority of cases of obesity in childhood arise from hypofunction or dysfunction of the thyroid gland, the hypophysis or both. However, with our more recent knowledge of the function of the nuclei in the hypothalamic region it is quite possible that disturbance of these centers, independent of the hypophysis, may result in obesity. Recent experimental work has shown that the thyroid gland and the hypophysis are intimately related physiologically and it is a fact that dysfunction of either one may secondarily affect the function of the other. Thus, hypothyroidism in childhood is characterized by retarded growth (the stimulation of growth being one pituitary function) and primary hypofunction of the anterior pituitary is frequently complicated by secondary hypothyroidism due to diminished secretion of thyroid stimulating pituitary hormone. It is important from a therapeutic standpoint, if possible, therefore, to determine which, primarily, is the disturbed organ.

HYPOTHYROIDISM AND OBESITY

If we consider the definition of obesity literally as meaning an increased storage of fat in the subcutaneous tissues of the body, most cases of hypothyroidism are not characterized by a true obesity, as the apparent obese appearance is in reality due to a boggy thickening of the skin and subcutaneous tissue nonadipose in character—a pseudo-obesity. However, in other but fewer instances there is in addition to the above an

increased deposit of subcutaneous fat due to lowered metabolism and decreased activity (more often present in the adult than in the child).

The typical appearance of hypothyroidism and obesity is the characteristic myxedematous, plethoric appearance of the face, thickened neck, increased prominence of the supra- and infra-clavicular fat pads, protuberant abdomen, short and broad hands and feet. However, the thickening and dryness of the skin is universal, no part of the body being exempt. Other important diagnostic features are the coarse, dry, brittle hair, phlegmatic attitude, coarse voice, frequent complaint of being cold in spite of adequate external heat, constipation, retarded physical growth and mental development, most marked in cases developing early in life. The degree of somatic retardation depends upon the age of onset and amount of active thyroid tissue present. Important laboratory features are roentgenographic evidence of retarded epiphyseal development and ossification, secondary anemia, lowered basal metabolic rate, elevation of serum cholesterol,⁹ decreased urinary excretion of creatine¹⁰ (both of which tend to return to normal following successful treatment with thyroid extract). A study of the serum cholesterol and creatine excretion are particularly valuable in infants and young children when the determination of the basal metabolic rate is impossible or unreliable. The change in creatine metabolism may be observed even before there is demonstrable change in the basal metabolic rate.

Milder or masked forms of hypothyroidism not infrequently follow infectious diseases in childhood and also occur at the pre-adolescent age in both sexes. They are usually evidenced by lessened physical and mental activity, the latter often not recognized until attention is called to the lack of satisfactory school progress. Moderate adiposity is frequently observed in these children together with changes in physical appearance. Early recognition should be emphasized in order that satisfactory treatment may be instituted. It should also be emphasized that in these children the changes from the normal variation in the metabolic rate, the blood cholesterol and the urinary excretion of creatine are often so slight that they alone will not give sufficient evidence to assure the diagnosis. The history

and clinical signs and response to therapy are, therefore, of greatest importance in establishing the diagnosis.

PITUITARY OBESITY

In an attempt to classify pituitary obesity, we are confronted with considerable difficulties. Unfortunately, we are not as yet far enough advanced to use the ideal classifications, namely, to correlate our clinical findings with the underlying pathology of the pituitary gland. Our knowledge of the normal physiologic functions of the various cellular pituitary elements is much too meager to ascertain with a reasonable degree of certainty the abnormal function of the various cells. However, there are certain illuminating facts worthy of mention.

Until comparatively recent years, disturbance of the posterior lobe was considered to be the only cause of most cases of pituitary obesity. However, since Cushing described the syndrome of pituitary basophilism confirmed at operation and at autopsy due to anterior lobe pathology and characterized by a typical obesity, we now know that this lobe also is involved in fat metabolism. Then, also, Anselmino and Hoffman¹¹ recently isolated a hormone from the anterior lobe which evidently is the regulator of fat metabolism.

To add to the confusion, Camus and Roussy¹² in Paris and Bailey and Bremer,¹³ Smith¹⁴ and others in this country have demonstrated experimental obesity in animals following injury to the superficial gray matter of the tuber cinereum near the hypophysis or to the hypothalamus with the hypophysis intact, indicating that in certain instances the pituitary alone is not directly responsible for endogenous obesity. Also, Walsh¹⁵ and others have reported rapidly developing obesity following encephalitis involving the midbrain.

In view of our incomplete knowledge, therefore, we are largely compelled to use clinical criteria for our classification whereby many difficulties are realized in relating clinical and laboratory data to findings which, naturally, are subjected to the individual interpretation of the observers.

Clinically we are able to distinguish the following types of pituitary obesity: basophilic adenoma of the pituitary (Cushing's syndrome); dystrophia adiposogenitalis (Fröhlich's syndrome); mixed thyroid and pituitary disturbances; other

conditions in which the pituitary gland may be involved: Laurence-Biedl syndrome, Dercum's disease (adiposis dolorosa) and other types of pituitary tumors.

1. **Basophilic adenoma of the pituitary (Cushing's syndrome, pituitary basophilism)** is characterized by adiposity, sexual changes, stunted growth, striations of the skin, hirsuties and hypertension. It is due to hypersecretion of the basophilic cells of the pituitary and probably to associated changes in the gonads and the adrenal cortex. The disease tends to occur in relatively young adults. Cases, however, have been encountered in children as young as six years of age. There is a predilection for females. If the disease occurs before puberty the sexual development is likely to be precocious. However, amenorrhea, frigidity and sterility in women and functional impotence in men develop early. The clinical picture is characterized by adiposity of a remarkably rapid onset, sometimes painful, which affects the head, neck and torso but leaves the arms and legs comparatively thin. There are typical bluish abdominal striae. In women and pre-adolescent males there is marked general hirsuties. The hypertrichosis is at first seen only on the body and in later stages there is growth of coarse hair about the face and chin as well. There is a plethoric appearance and polycythemia. The disease undoubtedly involves other endocrine glands in the form of a stimulation. The effect upon the parathyroid glands is indicated by osteoporosis, a negative calcium balance and increasing bone absorption. Involvement of the islands of Langerhans causes glycosuria and hyperglycemia at times leading to frank diabetes, a type particularly difficult to control with insulin. A secondary hyperplasia of the adrenal cortex may be evidenced by hypertension, a moderate hypercholesteremia, as well as by pigmentation of the skin and marked asthenia. Some of the most common complaints are extreme fatigability and weakness, abdominal and especially lumbosacral pains and violent intermittent headaches. *x*-Ray examination of the sella turcica usually reveals no expansion of the pituitary.

Laparotomy may be indicated if adrenal neoplasm is suspected. The treatment recommended is deep *x*-ray therapy and, when possible, early surgical removal of the tumor.

2. *Dystrophy adiposogenitalis* (Fröhlich's syndrome) is a dysfunction of the pituitary gland involving the anterior and intermediary (posterior) lobes and in all probability there is also a disturbance of the adjacent structures in the hypothalamic region. The onset of the disease may occur at any age, although usually it is not recognized until late childhood or adolescence. It occurs more often in females than in males, but in practice males are seen more frequently than females because their genital hypoplasia is more obvious. The hereditary predisposition of the disease cannot be overlooked, as frequently more than one member of the family is afflicted with a similar or some other glandular disturbance. Further proof of the frequent hereditary tendency is the fact that clinical changes may be observed in early infancy before extraneous factors could possibly have been the cause.

In Fröhlich's original description, pituitary tumor was the etiologic factor. However, we now know that intracranial hemorrhage involving the pituitary and its surrounding structures, encephalitis or possibly toxic suppression or degeneration following infectious disease, may result in this clinical syndrome. Also there are many instances in which no pathologic lesion is demonstrable clinically or at autopsy. It has been our experience that the majority of cases fall into this group.

The question has been raised whether other glands, such as the gonads or adrenal cortex, may be causative factors which secondarily influence the pituitary gland and a good deal of evidence has been accumulated to suggest that such may be the case (Wolf¹⁶).

Retarded sexual development, an outstanding feature of the disease, is a result of hypofunction of the basophilic cells of the anterior lobe with subsequent diminished or failure of gonadotropic hormone secretion. The resulting clinical picture depends upon the age of onset. Shortness of stature is more frequent when the onset occurs before puberty. However, less frequently there may be increased activity of the acidophilic cells with excessive growth. In the male, if the disease begins in early childhood or before the advent of puberty, the penis and scrotum remain very small. The testes are hypoplastic and frequently fail to descend. In the male

there is a tendency toward female configuration of stature. There is an increased accumulation of fat in the pubic region and in the older boys the distribution of pubic hair is of the feminine type.

When the disorder occurs in females, there is also retarded sexual development. In the younger child the diagnosis is frequently difficult because the sexual apparatus is not conspicuous. In the adolescent or older female, menstruation may never appear or may be delayed and irregular. The secondary sex characteristics fail to appear or are not fully developed.

The abnormal accumulation of fat, which also is characteristic of the disorder, is due in a major part to a *deficiency of the intermediary (posterior) lobe or disturbance of the structures located in the hypothalamic region*. There is rarely a history of excessive weight at birth. More often the parent complains that there was a rather sudden and progressive increase in weight beginning between the ages of seven and ten years. The weight may remain stationary for several months or years or may increase excessively practically uninterrupted into adulthood. The fat accumulation at times is enormous and is almost universally described as of the girdle type, characterized by a predilection for the pectoral and abdominal regions, the hips, thighs and upper arms. The forearm and legs remain free and appear slender in contrast.

These patients are usually endowed with normal intelligence but may be lazy or placid. Occasionally they are introspective and assume a seclusive attitude.

The biochemical changes that are frequently found associated with adiposogenital dystrophy are a result of the combined disturbance of the anterior lobe, the intermediary lobe and the hypothalamic structures. In spite of the fact that various hormones have recently been isolated from the anterior lobe which influence metabolism, it is, nevertheless, difficult to attribute any one particular phase of abnormal metabolism to an individual cellular element of the pituitary. However, it is generally agreed that hypofunction of both the anterior and intermediary lobes results in an increased carbohydrate tolerance probably due to a decrease in the secretion of an insulin antagonizing hormone (which in all probability has a

single origin somewhere in the anterior lobe¹⁷). Anterior lobe hypofunction may also result in a diminished secretion of the fat metabolism hormone with a resulting disturbance of normal fat metabolism. The basal metabolic rate is most often below normal but may be normal or elevated. The thyroid may be secondarily depressed as a result of the pituitary disturbance or there may be a coexisting primary hypothyroidism. The disturbed water and salt metabolism resulting in retention of fluids within the tissues or less commonly in diabetes insipidus is a result of the disturbance of the posterior lobe or the hypothalamus. Other metabolic changes that are frequently observed associated with this syndrome are the elevation of blood chlorides, the increased excretion of uric acid and a decrease of specific dynamic action of protein.

The prognosis of the disease depends primarily upon the underlying pathology. In the presence of a neoplastic disease or injury to the hypophysis, the outlook is obviously less encouraging. In our experience the most satisfactory recoveries occurred in those individuals in whom no evidence of organic disease was present. The earlier the diagnosis is made and the sooner treatment is instituted, the more favorable the prognosis. Coexisting thyroid involvement adds to the unfavorableness of the outlook.

Dysfunction of the anterior lobe of the hypophysis without definite evidence of posterior lobe involvement may be associated with obesity. Clinically it should be realized that in anterior lobe pathology there may be either hyperfunction or hypofunction of the various cellular components. Thus, the clinical picture may be one of excessive or retarded growth—precocious or retarded sexual development.

Posterior lobe hypofunction without clinical signs of anterior lobe involvement may also be associated with obesity. There are certain cases of adiposity in which the abnormal accumulation of fat is confined principally to the pectoral and girdle regions, the extremities remaining free, accompanied by evidence of posterior lobe involvement, such as increased dextrose tolerance, salt and water retention and at times edema and abnormal fat metabolism. In this group growth is usually normal and there is no evidence of genital dystrophy. Such cases are frequently and unjustly classified as Fröhlich's syn-

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These patients are usually endowed with normal intelligence but may be lazy or placid. Occasionally they are introspective and assume a seclusive attitude.

The biochemical changes that are frequently found associated with adiposogenital dystrophy are a result of the combined disturbance of the anterior lobe, the intermediary lobe and the hypothalamic structures. In spite of the fact that various hormones have recently been isolated from the anterior lobe which influence metabolism, it is, nevertheless, difficult to attribute any one particular phase of abnormal metabolism to an individual cellular element of the pituitary. However, it is generally agreed that hypofunction of both the anterior and intermediary lobes results in an increased carbohydrate tolerance probably due to a decrease in the secretion of an insulin antagonizing hormone (which in all probability has a

single origin somewhere in the anterior lobe¹⁷). Anterior lobe hypofunction may also result in a diminished secretion of the fat metabolism hormone with a resulting disturbance of normal fat metabolism. The basal metabolic rate is most often below normal but may be normal or elevated. The thyroid may be secondarily depressed as a result of the pituitary disturbance or there may be a coexisting primary hypothyroidism. The disturbed water and salt metabolism resulting in retention of fluids within the tissues or less commonly in diabetes insipidus is a result of the disturbance of the posterior lobe or the hypothalamus. Other metabolic changes that are frequently observed associated with this syndrome are the elevation of blood chlorides, the increased excretion of uric acid and a decrease of specific dynamic action of protein.

The prognosis of the disease depends primarily upon the underlying pathology. In the presence of a neoplastic disease or injury to the hypophysis, the outlook is obviously less encouraging. In our experience the most satisfactory recoveries occurred in those individuals in whom no evidence of organic disease was present. The earlier the diagnosis is made and the sooner treatment is instituted, the more favorable the prognosis. Coexisting thyroid involvement adds to the unfavorableness of the outlook.

Dysfunction of the anterior lobe of the hypophysis without definite evidence of posterior lobe involvement may be associated with obesity. Clinically it should be realized that in anterior lobe pathology there may be either hyperfunction or hypofunction of the various cellular components. Thus, the clinical picture may be one of excessive or retarded growth—precocious or retarded sexual development.

Posterior lobe hypofunction without clinical signs of anterior lobe involvement may also be associated with obesity. There are certain cases of adiposity in which the abnormal accumulation of fat is confined principally to the pectoral and girdle regions, the extremities remaining free, accompanied by evidence of posterior lobe involvement, such as increased dextrose tolerance, salt and water retention and at times edema and abnormal fat metabolism. In this group growth is usually normal and there is no evidence of genital dystrophy. Such cases are frequently and unjustly classified as Fröhlich's syn-

drome. The basal metabolic rate may be within normal limits. The history is that of a gradual onset as contrasted with the more rapid onset and more striking obesity that follows injuries to the tuber cinereum or the hypothalamus (Cushing).

3. Mixed Thyroid and Pituitary Disturbances.—These terms in the strict sense do not impart any great significance, because, as previously mentioned, our newer knowledge concerning the function of the endocrine glands has shown us that a true monoglandular disorder is not the rule, as a disturbance of any one gland frequently affects the function of another.

In infancy the thyroid symptoms usually predominate over the pituitary and in late childhood and adolescence more likely the pituitary symptoms predominate over the thyroid.

Thyropituitarism differs from true myxedema or cretinism with growth retardation in that true obesity is usually a prominent feature, as contrasted with the pseudo-obesity of myxedema. Clinically, these children usually present the combined picture of hypothyroidism and adiposogenital dystrophy. The diagnosis is made on the history of symptoms of hypothyroidism in infancy preceding the development of pituitary symptoms. One cannot overemphasize the importance of an accurate case history as frequently the early symptoms of hypothyroidism may be overlooked, especially when they are not classically those of cretinism or myxedema as previously described. Symptoms such as retarded average normal developmental progress in early infancy, retarded mental progress and roentgenographic evidence of delayed epiphyseal growth and ossification are indicative of infantile hypothyroidism.

In the older child, adolescent or adult, mixed thyroid and pituitary disturbances may be present either as a dysfunction of the anterior lobe (without posterior lobe signs) complicated by secondary hypothyroidism, or as adiposogenital dystrophy with coexisting hypothyroid manifestation. After years of showing evidence of anterior lobe dysfunction, viz., growth disturbance, sexual retardation, and often obesity, etc., signs of hypothyroidism complicate the picture. This in all probability is due to a failure of adequate thyrotropic hormone secretion by the hypophysis. There may or may not be retarded growth of stature, depending upon the activity of the acidophilic cells of the anterior lobe. The basal metabolic rate is below the

lower limits of normal. A further confirmation of the diagnosis is the failure of response to the thyroid extract alone, and the response to the combined administration of thyroid extract with anterior pituitary thyrotropic hormone or extract of the whole anterior lobe.

4. Other Conditions in which the Pituitary Gland May Be Involved.—Laurence-Biedl Syndrome.—This condition has many of the features of the Fröhlich type. The adiposity and genital dystrophy are further complicated by mental deficiency, retinitis pigmentosa, polydactylism and often other congenital anomalies. The obesity is of the "girdle" type.

Underfunction of the anterior lobe of the pituitary has been the most commonly accepted theory advanced. More recently, mechanical destruction of the tuber cinereum or congenital defects in the trophic centers of the hypothalamus have been suggested as the seats of the underlying pathology.

Dercum's disease (adiposis dolorosa) is characterized by painful localized deposition of fat, asthenia, and psychic disorders, rarely seen in children. It occurs most frequently in women of middle age. It is thought that its origin may be due to pituitary hypofunction. The adiposity consists of large lipomatous nodular masses, separated usually by deep furrows mostly in the upper arms, the thighs, the inner aspects of the knees and the lower abdomen, producing a large pendulous apron of fat.

GONADAL OBESITY

Obesity due to primary involvement of the sex glands should be mentioned, although it rarely occurs in childhood. The rôle of the sex glands in the development of obesity has not been definitely established, although in all probability the effect is due to a disturbance in the normal function of the pituitary or thyroid glands. Gonadal obesity usually arises after operative or irradiation castration. Primary failure of the male gonads is exceedingly rare in childhood, but may follow injury or epidemic parotitis. Primary ovarian failure also seldom occurs in childhood. Primary failure of the gonads in late childhood or adolescence is rarely associated with obesity but usually with malnutrition, whereas in the adult obesity is usually present. The adiposity is characteristically found in the trochanteric regions.

The diagnosis of primary gonadal failure and obesity should be made only after the exclusion of all other causes and by the possible history of injury to the gonads or previous epidemic parotitis. To exclude the possibility of primary pituitary insufficiency, a study of the urinary excretion of gonadotropic hormone may be helpful as in this condition there is a decrease or absence of hormone in the urine, whereas in the primary gonadal failure (castration and menopause) there is an increased excretion of hormone.¹⁸

ADRENAL OBESITY

There are certain pertinent facts known concerning diseases of the adrenal cortex in children. Cortical tumors leading to hyperfunction of the organ are accompanied by precocious development of the entire body, especially of the sex glands. If such tumors arise in the fully mature body, sex gland activity is impaired and obesity frequently develops. In children there have been rare cases of cortical hyperplasia and tumor presenting a picture similar to Cushing's syndrome, a plethoric type of obesity with hirsutism and a tendency to the development of characteristics of the opposite sex. Diagnosis can be made only by exclusion of all other causes of obesity and exploratory laparotomy.

PANCREATOGENIC OBESITY

Falta says: "Primary enhanced function of the islet system may play a part in causing obesity since it permits abnormally easy assimilation of excessive amounts of food." The increased appetite which leads to obesity might often be due to augmented islet function, which may be artificial or spontaneous hyperinsulinism (mild or moderate forms). There have been cases of islet carcinoma described in adults in which obesity developed instead of the usual wasting. However, at present there are no definite clinical diagnostic criteria to indicate a diagnosis of pancreatogenic obesity.

TREATMENT OF OBESITY

In considering the treatment of obesity in any child, it must be realized that there is always the possibility of spontaneous regulation and correction of the underlying metabolic

or endocrine disturbance. Not uncommonly during the rapid physiologic changes of puberty and adolescence, adiposity gradually disappears. Also during these periods there is normally a pronounced stimulation and increased activity of the sex glands so that what may be considerably retarded sexual development in childhood is often spontaneously corrected during adolescence. On the other hand, parents bring their children to the physician to correct an existing condition; therefore, the child must be treated. Also, are we as physicians justified in waiting months or years for a possible spontaneous correction of a definite endocrine condition?

Dietary Management.—It is generally agreed that, regardless of the underlying causes of obesity, dietary restriction is of the greatest importance. Whether obesity is hereditary or constitutional, hyperalimentary or endocrine in origin, a state of overnutrition exists for that particular child. In other words, there is an excess of intake over the caloric requirement.

A careful family history for the possibility of endocrine or metabolic disorders, a developmental history, a survey of the family and patient's food habits are taken into consideration. A complete physical examination and necessary laboratory examinations must be made. If there is no indication of endocrine dysfunction, the treatment consists primarily of dietary management. If the obesity is on the basis of endocrine dysfunction, dietary management and endocrine therapy are indicated.

The majority of obese children have a healthy or excessive appetite. The child enjoys eating and his will power is poor. The appetite is frequently a question of satiation. We are, therefore, confronted with the problem of furnishing a low caloric diet that is palatable and "filling"—a diet that will satisfy the patient and meet the basal requirement for the child's weight and height. The diet must contain adequate protein, minerals and vitamins for growth and development.

We realize, as have others, that in prescribing a reducing diet for a child, we are confronted with special problems. Among these problems are difficulty in reducing the food intake of children with good appetites, overcoming capricious appetites, and satisfying those with not large but finicky appetites. Most children, even those with anorexia, love

sweets and we know that school children obtain candy, cookies and other foods from sources outside their homes. Secondly, we face the problem of obtaining cooperation from the parents. They do not want their children to be fat and yet often they are unable to withstand the child's requests for foods other than those prescribed. Therefore, it is of paramount importance that the maximum amount of cooperation be obtained from the child and also full cooperation and support from the parents. The cooperation of the child may frequently be obtained by explaining the purpose of the diet, and by psychologic approach, describing, if necessary, the relationship of fatness to poor health and to an unhappy social existence. In this way it is usually possible to obtain the cooperation of older girls, as they have more pride in their personal appearance than boys.

We have found that when the child has been on the special diet provided for a variable period of time, his desire for sweets and other prohibited foods gradually diminishes and a time is frequently reached when there is no longer a craving for prohibited food and the matter of adhering to the diet requires less effort.

We have found, as others have,¹⁹ that a *high protein diet* is of decided value in the treatment of obesity. The high protein content of the diet tends to keep the basal metabolic rate elevated by virtue of its specific dynamic action, offsetting the lowering of the basal metabolic rate, which would result from a long-continued low total caloric intake.⁸ By increasing the protein, the diet can be made more palatable and will satisfy the patient. With the protein high, the fat proportion is kept low and as a result the patient's own body fat is in part utilized.

The high protein-low caloric diet should furnish at least 2 to 2½ Gm. of protein per kilogram of body weight of the child. The fat is cut down as much as possible, even to the giving of skimmed milk. Carbohydrates are added to bring the number of calories to the total computed for the particular child according to age, height and average weight. The feeding of vegetables and fruits containing the least amount of carbohydrates but still furnishing a large amount of bulk and minerals is encouraged. An increase in calories can be ad-

justed according to the rate and degree of weight loss. Vegetables and fruits of greater carbohydrate percentage may be substituted and 1 to 2 squares of butter or whole milk will supply additional fat. Unsweetened jello serves as one of the suitable desserts. If a child must take his lunch to school from home, the diet is so arranged as to make this practical.

The temporary *restriction of total fluids* to 800 to 1000 cc. daily is helpful in preventing water retention in the body tissues. In the active child in whom there is greater energy consumption, less rigid restriction is permissible.

The high protein diet in itself is usually sufficient to promote *dehydration*. Clinically, we have noted the common complaint of mothers of our celiac patients of frequent and excessive urination by their children on the high protein diet used in the treatment of these cases. Foldes²⁰ offers an explanation for this phenomenon. In discussing the physiology and pathology of general water metabolism in his article on the antiretentional dietary treatment of migraine, he states that increased diuresis produced by a diet rich in protein is due to two factors: one, the presence of a high percentage of urea which is known to be one of the strongest and most effective diuretics, and the other the high percentage of nucleoproteins containing purine substances, which are chemically related to the diuretics of the caffeine group. On the contrary, high carbohydrate and fat-rich diets favor the retention of fluids.

Recently Barker²¹ found that edema could be controlled satisfactorily in a large percentage of cardiacs and nephritic patients by the *restriction of sodium chloride* and the *substitution of potassium chloride* in the diet to approximately that of the average normal diet, namely, about 3.5 Gm. per day, and providing a full general diet with an acid ash excess. He was unable to explain this phenomenon.

Both Rusk^{19c} and Baumgarten^{19b} capitalized on Barker's observation and have successfully treated obesity by the high protein and high potassium-acid ash diet.

It should be mentioned that excessive amounts of potassium may produce toxic effects and, therefore, the potassium salts should be used with caution.

In some of our cases we restricted sodium chloride and used potassium in the form of potassium acetate 5 to 10 grains

three times daily, the acetate having the advantage over the chloride because of its diuretic effect.

Endocrine Therapy.—The value of endocrine therapy in the management of obesity has always been a matter of considerable controversy which, in a large part, is due to our incomplete knowledge concerning the physiology of the endocrine glands and their relationship to obesity. Also, as previously mentioned, the hypothalamic region may play an important rôle in certain types of adiposity. Our greatest stumbling block, therefore, is our meager understanding of the hypophyseal-hypothalamic relationship in metabolism and obesity. Nevertheless, it has been our clinical experience that endocrine therapy is definitely beneficial in certain types of obesity.

Thyroid Therapy.—It is generally agreed that thyroid substance is specific in the treatment of primary hypothyroidism. The dose will vary with the ages of the child, the severity of the clinical symptoms and individual sensitivity. The amount and duration of the therapy should be controlled by evidence of clinical improvement, the rise in the basal metabolic rate, the fall in the serum cholesterol and the increase in the urinary excretion of creatine. In many of our cases of hypophyseal obesity the basal metabolic rates were definitely below normal, which might be explained by a diminished thyrotropic hormone secretion secondary to hypophyseal dysfunction. We believe, in addition to pituitary therapy, thyroid extract is indicated in these cases. The thyroid gland prescribed must also vary in amount according to the age, the clinical evidence as to the degree of thyroid hypofunction and the overweight of the individual child. It is good policy to start with minimum amounts, gradually increasing the dose, which should be largely dependent upon the clinical result attained. The daily dosage will vary from as low as $\frac{1}{2}$ up to 2 to 5 grains. The patient should be seen weekly and the weight and pulse recorded. Depending upon age and degree of overweight, an early weekly weight loss of from 1 to 3 pounds may be considered as not excessive. Palpitation, persistent rapid pulse and other untoward reactions should lead to a reduction or elimination of the thyroid therapy.

We also believe that some obese children with normal basal metabolic rates may receive small doses of thyroid to advan-

tage in view of the fact that the basal metabolic rate tends to fall as a result of a long-continued low caloric diet. Wang, Strouse and Saunders have shown that the specific dynamic action of the proteins is diminished in the obese child and the metabolism stimulating effect is minimum.⁸

Pituitary Therapy.²²—*Whole anterior lobe extract* may be used to compensate for endocrine deficiency in which there appears to be diminished secretion of the hormones of the entire anterior lobe. One half to 2 cc. subcutaneously are administered at least twice weekly. While there is considerable difference of opinion as to the value of the desiccated anterior lobe by mouth, we believe that 5 or 10 grains three times daily has been of value in some of our cases either alone or when given in addition to the above.

Sex Hormones.—In the presence of retarded sexual development, the pituitary preparations should be complemented by the gonadotropic hormone from pregnancy urine or from placenta in doses of $\frac{1}{2}$ to 2 cc., two or more times weekly. The advantage of combining pituitary extract with the pregnancy urine or placental extracts is probably due to the synergist present in the pituitary extract which augments the action of the prolan present in the latter. We are not as yet in position definitely to evaluate the results following hypodermic administration of some of the newer gonadotropic fractions of the anterior pituitary which have been placed at our disposal for clinical study of sexual infantilism and cryptorchidism.

Growth hormone may be used in conjunction with other preparations in the presence of retarded growth of stature before closure of the epiphyses. Our limited experience with growth hormone does not warrant our making any statements as to results at this time.

Thyrotropic Hormone.—When pituitary dysfunction is complicated clinically by secondary hypothyroidism, thyrotropic hormone 1 to 2 cc. three times weekly should be administered in addition to thyroid extract. Our experience with thyrotropic hormone has been limited to a few cases; nevertheless, we believe that it has definite possibilities for the treatment of such cases.

Posterior Lobe Extract.—For many years posterior lobe extract has been advocated for the treatment of obesity. We

have not seen any benefit from the use of posterior lobe preparations in the treatment of obesity, and from a physiologic standpoint the use of pituitrin is contraindicated as it is antagonistic to insulin which is a powerful metabolic stimulant. Posterior lobe extract may be indicated, however, in the rare cases of obesity with coexisting diabetes insipidus. In such cases, pitressin hypodermically or intranasally, or desiccated posterior lobe powder intranasally may be of value in controlling the polydipsia and polyuria. A number of pharmaceutical firms produce posterior lobe preparations for hypodermic use which have been accepted as official by the U.S.P. Some of these contain both fractions; others the pressor or the oxytocic alone.

The hypodermic administration of the various pituitary extracts should be limited to courses of from four to six weeks. There should be intervening rest periods of from two to four weeks in order that the production of antibodies or antihormones may be minimized.²³

Gonadal Hormone Therapy.—Ovarian and testes hormones have been used for both primary and secondary hypogonadism in the adult female and male respectively with varying degree of success. Estrogenic and lutein hormones have been administered for various menstrual disorders, the menopause, etc., replacement therapy has been attempted following castration, and in the male testes hormone has been administered for the relief of sexual infantilism, impotence, aspermia (sterility), prostatic hypertrophy, etc.

In view of the fact that primary hypogonadism is extremely rare in childhood, these preparations should be used with caution, if at all, as both the female and male sex hormones in large doses are antagonistic to the pituitary.²⁴

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 d. Baumgarten, W.: Southern Med. Jour., 28: 169 (Feb.), 1935.
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22. Some of the available endocrine products for hypodermic administration which we have used are:
 1. Pituitary—anterior lobe—hormones from bovine glands.
 - Whole anterior lobe:
 - Antuitrin (Parke-Davis) (mainly growth and some luteinizing hormone).
 - Anterior pituitary extract (Squibb) (mainly growth).
 - Polyansyn (Ayerst).
 - Growth factor:
 - Antuitrin G (Parke-Davis).
 - Phyone (Wilson).
 - Growth factor (Ayerst).
 - Gonadotropic factor:
 - Maturity factor (Ayerst).
 - Prephysin (Chappel) (pituitary and serum combination).
 - Hebin (Wilson).
 - Thyrotropic factor:
 - Thyreotropic hormone (Ayerst).
 2. Pituitary—posterior lobe.
 - U.S.P. products made by many firms.

3. Anterior pituitary-like gonadotropic factor.

Pregnancy urine extract:

Antuitrin S (Parke-Davis).

Follutein (Squibb).

Antophysin (Winthrop).

Placental extract:

A.P.L. (Ayerst).

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CONTRIBUTION OF DR. BUDD C. CORBUS

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SEROLOGICAL CONTROL OF NEISSERIAN INFECTIONS BY MEANS OF THE BOUILLON FILTRATE (CORBUS- FERRY)

STATISTICS record that about 800,000 cases of gonorrhea are reported in the United States yearly. It is estimated that between 2000 and 4000 occur that are not recorded.

It is a long time since the gonococcus was discovered by Neisser, but in this period there have been many attempts to standardize a rational method of treatment. One has only to read part of the many publications on treatment to realize that standardization of the treatment of gonococcal infections does not exist.

For years some form of local treatment has been employed in attempting to cure this infection. Of late silver salt derivatives were preferable. The success or failure of this method depended, as a rule, upon the concentration of the preparation and the frequency of application.

In the fall of 1929 a definite attempt was made to attack the problem in an entirely different manner.

During the last ten years three methods of approach have been opened, all of which are related to or based upon the defensive mechanism of immunity in man. These are comprised, first, of the cells that are immunized (the reticulo-endothelial system); second, of the route of introduction of the immunizing agent (the skin), and third, of the immunizing agent (bacteria or their toxins).

1. **The Reticulo-endothelial System.**—The reticulo-endothelial system was recognized as early as 1884 by Metchnikoff¹ who called its cells "macrophages." However, Aschoff,² in 1914, emphasized the cellular mechanism of defense that char-

acterizes these cells. Since then Metchnikoff's original conception of immunity has been accepted as a rational defensive mechanism. To avoid confusion in this paper the term "histiocytes," as suggested by Maximow,³ will be used. These cells are found in the spleen, liver, lungs, omentum, bone marrow, lymph nodes, and in the true skin. This large group of cells constitutes the defensive mechanism against disease in the human organism that reacts precisely the same to stimuli, no matter through what portal of entry they are introduced.

When antiseptics are applied to the mucous membrane or broken skin, if not too concentrated, they only stimulate the histiocytes to become more sensitive. There is, however, no specific affinity between the cells and the invading organism. If applied too often and in too concentrated solution, they produce local engorgement of the tissue often followed by necrosis.

2. The Skin (the Route of Immunizing Agent).—The skin is to the body as the von Hindenberg line was to the German Army during the war. When there is an injury to the skin, communication by means of the nervous system is established between the defensive mechanism in the skin and the bone marrow. Cells are mobilized and brought to the site of the injury. It is in the true skin that the tools are found and materials utilized to bring the body's defensive mechanism into action (Fig. 31).

Scientifically, the procedure of influencing disease by way of the skin was introduced by Jenner⁴ in 1796. He seemed to have been fully conscious of the importance of the skin in the prevention and cure of disease. The skin acts as an amplifier of specific and nonspecific irritants (proteins). The response to stimuli introduced intradermally, according to E. F. Müller,⁵ is from 100 to 150 times greater than that produced by any other than the intravenous route.

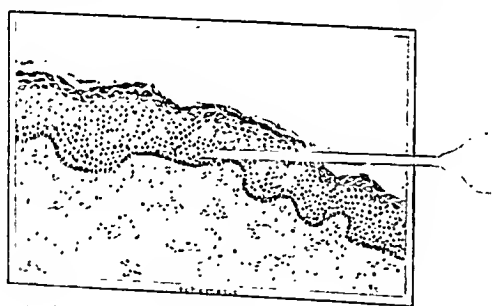
3. The Immunizing Agent.—Stimulated by the work of Besredka⁶ in specific immunization by his "antivirus," we directed our attention, in the fall of 1929, to the possibility of producing a gonococcal antigen solution. Having failed in this attempt, the assistance of Clark and Ferry of the Research Department of Parke, Davis and Company was obtained. They produced a gonococcal bouillon filtrate and

found that it contained a soluble toxin and that it was not an antiviral. In December, 1930, before the Society of American Bacteriologists,⁷ they presented their paper on studies of the properties of a bouillon filtrate of the gonococcus, the conclusions of which are as follows:

Intradermal injection



Immunological response to proteins introduced intradermally is greater than that produced by any other route except the intravenous.



Note rich vascularity of true skin.

Fig. 31.

1. The gonococcus produces an extracellular toxin, when grown in suitable liquid medium, which promotes rapid development.
2. The sterile bouillon filtrate from young cultures contains this extracellular toxin in sufficient concentration to give positive skin reactions in dilutions of 1:100 to 1:1500.

3. Injection of animals with this toxin stimulates the formation of an antitoxin which will neutralize the toxin *in vitro* as well as *in vivo*.

4. Control autolysates and mechanically produced control intracellular extracts give negative skin reactions in low dilutions.

Since 1931 gonococcus bouillon filtrate has been used by many physicians in the United States, Canada and our island possessions.* In answer to a questionnaire mailed in 1936 to 850 physicians, members of both the American Urological Society and the American Neisserian Society, there were replies from 478 physicians, 42 per cent of whom had no experience, 40.4 per cent had favorable results, 12.1 per cent claimed unfavorable experiences, while 5.5 per cent were in doubt. In all there were 9662 cases treated. The ratio of favorably treated cases to unfavorably treated cases was 4.75:1. Thirty-six physicians, reporting 1611 cases, stated that their results were uniformly more favorable in acute and chronic infections in men and women than with any other method.

The defensive mechanism of immunity in man having been established, a toxin discovered, the safest method of introducing it established, why has it met with failure in some instances?

Experience marks the advance in any new biological. That patients have been overimmunized by myself and others there can be no doubt. Up to the present time dosage was governed entirely by clinical results. Often this was startling. However, many times it was most discouraging. Overimmunization often occurs.

Until now we have had no method of determining when a given individual had received enough of the toxin. Many times he was placed in a state of disimmunization (comparable, as Kahn states, to disarming a soldier in battle).

For many years we have been familiar with the fact that a positive complement fixation test *does not occur* in gonorrhea, either acute or chronic, except during systemic invasions, *i. e.*, gonorrheal septicemia, tubal infections, severe prostatic infections especially abscess, pyelitis, arthritis and endocarditis.

A given patient with a positive complement fixation test is in a state of hypersensitivity to the gonococcus. He is hypo-

* Corbus, B. C.: The Southern Med. Jour., 29: 710-715 (July), 1936

sensitized to the gonococcus by giving the toxin intradermally.

A given patient with a negative complement fixation test is injected until he is in a state of hypersensitivity and continued on the same management until hyposensitization is complete (negative complement fixation).

This is comparable to desensitizing a patient with asthma, who has a hypersensitivity to eggs, with small, initial doses of egg white.

Acute Case—Plan of Treatment

First week (also first day):

1. Gram stain examination, or culture.
2. Complement fixation test for gonorrhea.
3. Therapeutic dose.

Second week:

1. Take complement fixation test BEFORE giving therapeutic dose.
2. Therapeutic dose:

Size of dose is governed by local tissue reaction. If the patient is seen twice a week, take complement fixation test *three* days AFTER therapeutic dose. If seen only once a week, take complement fixation test BEFORE therapeutic dose is given.

Third week:

1. Repeat.

Fourth week:

1. Repeat, etc.

Note.—As the size of the dose is increased and the general immunity is acquired, the complement fixation test will become first 1 plus, then 2 plus, later 4 plus. Then all of a sudden it will return to a negative. Notwithstanding, there may still remain a slight discharge with shreds in the urine. Occasionally it is impossible to obtain a 4 plus positive complement fixation test. If at any time the complement fixation test turns from a 1 plus or 2 plus positive to a negative test, stop injections and await clinical symptoms. It may still be necessary to give one or two intracutaneous injections (0.2 or 0.25 cc.) to effect a permanent cure. Where there is any possible suspicion of prostatic or even posterior involvement, gentle massage should be given once a week.

Local Treatment.—No local treatment or medication of any kind is given except sedatives where indicated. The use

of haliver oil with viosterol is substituted for the old time balsam medication.

The ingestion of 5 to 7 glasses of water a day is imperative.

Good drainage must be provided for by the wearing of a gonorrheal bag, also a suitable suspensory to avoid epididymitis.

The fact that the patient is under immunization management does not lessen the dangers of overactivity while the disease is being treated. I have found the following prescription of value as a urinary sedative:

R Codeinae sulphatis	0.25
Tincturae hyoscyami	15.00
Syrupi gaultheriae	30.00
Aquae gaultheriae	q.s. ad. 120.00

M. et Sig: One teaspoonful in water q. 4-6 hours.

Chronic Case—Plan of Treatment

Proceed as with the acute case. If by chance the complement fixation test is positive from the beginning, treat the patient with filtrate until a negative is obtained. Then stop and await clinical results.

After two or three weeks have elapsed following cessation of all intradermal medication, it may still be necessary to give one or two intracutaneous injections (0.25 or 0.3 cc.) to effect a permanent cure. This, however, should not be done until sufficient time has elapsed to completely evaluate the method.

Suggestions.—In addition to the directions that accompany each package of bouillon filtrate an added experience has enabled me to make the following suggestions in dosage.

The size of the first dose is in direct proportion to the duration of the infection, *i. e.*,

First week	0.1 cc.
Second week	0.25 cc.
Third week	0.2 cc.

However, never commence treatment with an initial dose larger than 0.2 cc. in a chronic case.

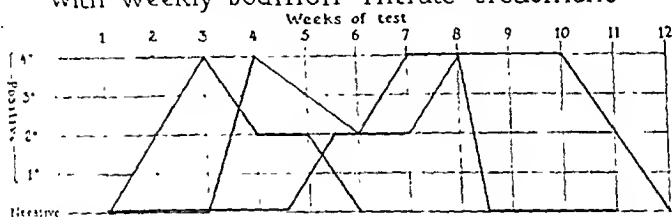
Following the first dose the size of the local cutaneous reaction should be used as a guide to future doses.

If the local tissue reaction after twenty-four hours is only 2 inches in diameter, increase the dose after seven days by 0.1 cc. If the local tissue reaction is from 2 to 3 inches in

diameter, do not increase the dose until the local tissue reaction after twenty-four hours is 2 inches in diameter or less. If the local tissue reaction is over 3 inches in diameter after twenty-four hours, decrease the dose by 0.1 cc.

DEPARTMENT OF PUBLIC HEALTH STATE OF ILLINOIS

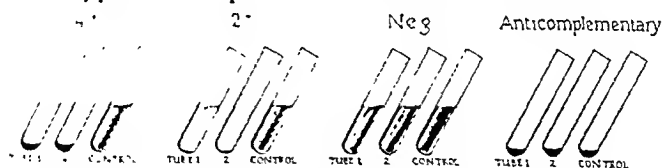
The complement fixation test in Neisserian infections
Typical Reactions
with weekly bouillon filtrate treatment



Procedure for complement fixation test

	Antigen	Patient's serum inactivated at 56° for 30 min	'Guinea pig' complement 2 units	Fixation	(Sheep cell antibodies) 2 units	(Sheep cell antibodies) 25% in saline	Incubation
Control	0	0.1 ml	0.1 ml	Overnight	0.25 ml	0.25 ml	30 min
Tube 2	0.05 ml	0.1 ml	0.1 ml	in	0.25 ml	0.25 ml	in
Tube 1	0.10 ml	0.1 ml	0.1 ml	refrigerator	0.25 ml	0.25 ml	water bath at 37° c

Typical complement fixation reactions



A positive complement fixation test for gonorrhea occurs only during systemic invasions such as *gonorrheal septicemia*, *salpingitis*, *severe prostatic infections*, *pyelitis*, *arthritis* and *endocarditis*. It is also positive when the patient is hypersensitized by treatment.

Fig. 32.

In order to determine accurately the size of the local tissue reaction after twenty-four hours, it is suggested that the patient trace the size of the inflammatory area with tissue or toilet paper, bringing the tracing to the doctor at his next visit.

Reactions are less severe following the cutaneous administration of bouillon filtrate if the injections are placed on the posterior surface of the arms or anterior surface of the torso.

Use a "tuberculin" syringe with a 27-gauge needle.

Note.—Put all intradermal injections at least 4 inches away from previous injections. Continued injection in the same area produces local immunity, thereby inhibiting absorption of the toxin.

The results of this standardized method of treatment of gonorrhea with the gonococcal bouillon filtrate have been so successful in my practice that it has been adopted as routine in the Evanston Social Hygiene Clinic for the following reasons:

1. Patients report for treatment but once a week.
2. No local treatment whatsoever is given; consequently, it entails less expenditure and is convenient for both patient and physician.
3. Complications are reduced to a minimum.

The complement fixation test is performed by the Illinois State Department of Health and is used as our standard (Fig. 32).

Complement Fixation Test for Neisserian Infection.—Any laboratory equipped to perform serologic tests for syphilis should be able to perform the complement fixation test for gonorrhea. In the April 10, 1937, issue of the *Journal of the American Medical Association*, page 1241, the test is described in detail.

In performing the test it is always desirable to have a known positive control. This is obtained by using Biological 96, Parke, Davis and Company.

As an antigen Biological 102, Parke, Davis and Company, can be procured if the laboratory is not familiar with preparing an antigen.

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CLINIC OF DR. VINCENT J. O'CONOR

WASHINGTON BOULEVARD HOSPITAL

CYSTITIS

WE have been asked today to give a clinic on cystitis. Cystitis is the term used to designate an infection of the urinary bladder. It is well to emphasize at the outset that cystitis is rarely a clinical entity. Infections of the bladder may be acute or chronic, superficial, interstitial or pericystic (involving the tissue surrounding the bladder).

Case I.—Unmarried female, twenty-three years of age, stenographer, has always been well except for repeated sore throat and upper respiratory infections the past three winters. General health excellent and no gastro-intestinal or menstrual disorders. Five days ago the patient was taken with a sudden severe chill on the elevated train returning home from work. On arrival at home feeling weak and tired, she was seized with sudden urgent desire to urinate. Urination was very painful with spasms of urethral discomfort following the act. Temperature was elevated to 101° F. and she had a constant desire to urinate every ten to fifteen minutes with severe strangury during the act. Her family physician was called and examined patient carefully. Throat was negative except for enlarged, slightly reddened, cryptic tonsils. Chest and heart normal. Abdomen was soft and there were no areas of tenderness in the renal areas or over abdomen. Voided urine appeared turbid and blood-tinged. Repeated doses of codeine and tincture of hyoscyamus only partially relieved the frequency and urgency, although the temperature returned to normal the next day and there has been no elevation since.

Patient was admitted to the hospital three days ago with the diagnosis of "cystitis." Examination shows a normal blood count, no leukocytosis. Urinalysis shows 2 plus albumin, no sugar, 500 pus cells and 25 red blood cells to the centrifuged specimen. Smears show many short rods and urine culture reveals a fine growth of *Escherichia coli* organisms. There is no residual urine in the bladder. Cystoscopy shows a diffuse hyperemia of the trigone, no submucous hemorrhages or edema, no stone, tumor or diverticulum. The right ureteral orifice is edematous, injected and pouting. Catheterization of the ureters shows a turbid purulent urine from the right kidney and a clear, normal-appearing urine from the left. Pus and colon bacilli in quantity from

the right; normal findings from the left. Dye output from either kidney is normal. Flat roentgenograms show normal renal outlines and no shadows suggestive of renal stone. Excretory urograms show normal-appearing renal pelves and ureters.

Urologic Diagnosis.—Right pyelitis, secondary cystitis, chronic tonsillitis (possibly the primary focus of infection).

Following ureteral catheterization patient's frequency and dysuria disappeared completely in twelve hours. She is now having ammonium nitrate, 15 grains three times daily, and ammonium mandelate, 4 Gm. daily.

This patient illustrates a typical clinical fact that, despite all absence of localizing clinical symptoms, the primary urinary disease was that of pyelitis and the cystitis was merely a secondary manifestation of this upper tract infection.

Case II.—Male, fifty-one years of age, lawyer, always well except for attacks of left renal colic five years ago, at which time 4 small stones were voided through the urethra. No subsequent renal colic and no dysuria or frequency. Present illness began while on a vacation in Italy five weeks ago, at which time a severe gastro-enteritis was followed by sudden onset of urgency, frequency and terminal dysuria. Terminal hematuria was noted on several occasions but no "port-wine" colored urine was passed. He had no pain in abdomen or renal regions, no chills or fever. Diagnosis of cystitis was made in Italy and confirmed by local physician. Patient has taken hexamethylenamine compounds, mandelic acid and sulfanilamide at various times with complete clearing of the urine but with no relief of frequency and urgency. He was admitted one week ago with diagnosis of "cystitis and prostatitis."

Examination is negative except for slight tenderness on deep pressure over suprapubic region. Prostate per rectum not enlarged and only 5 to 10 leukocytes per high power field in the prostatic strippings. Urinalysis shows 1 plus albumin, no sugar, 5 to 10 pus cells and 10 to 15 red blood cells per high power field in the centrifuged sediment. A few gram-positive cocci were found on direct urinary smear. Plain roentgenogram shows normal renal outlines and no shadows suggestive of stone in renal or ureteral regions. In the suprapubic region there is an oval density 2.5 cm. in diameter. Test for residual urine shows only 10 cc.

Cystoscopy shows normal urethra, no obstructing prostatic tissue but a bladder calculus corresponding in size to the shadow seen in the previous film. Urine from either kidney is normal and uninfected and the dye output is normal. The bladder stone was crushed under vision with the cystoscopic lithotrite and the fragments removed by suction and washing. An indwelling catheter was left in place for forty-eight hours. Patient is now voiding freely and without distress, although a moderate increase in frequency persists. Excretory urograms are normal.

Urologic Diagnosis.—Vesical calculus (probably an enlargement of a stone previously passed into the bladder from the left kidney five years ago and not voided per urethram); secondary cystitis

Both of these patients illustrate the secondary nature of "cystitis."

Etiology.—The common routes of infection are from the kidneys by way of the ureter and by direct extension from the posterior urethra. Less common routes are by the blood stream (hematogenous) and by fistulas between the bladder and some adjacent structure. The normal bladder is very resistant to bacterial invasion, and inflammation of the bladder usually implies prolonged or severe descending infection, retention of urine, congestion or predisposing trauma such as follows the urethral passage of sounds, catheters or other instruments.

The infecting organisms correspond with those of the kidney and renal pelvis above but with the addition of the gonococcus, which in fact invades the trigonal structures, rarely produces a diffuse cystitis. Syphilis of the bladder, amebic cystitis and bilharziasis are very rare conditions, except in isolated localities and are hematogenous in origin.

The predisposing factors which favor localization of bacteria in the bladder are: (1) all the various causes of residual urine; (2) pregnancy, cold, foci of infection, and (3) trauma from prolonged overdistention (as after surgical operations) and the introduction of unclean instruments or strong corrosive solutions.

Causes of Residual Urine in Bladder.—*Common to Male and Female.*—*Bladder:* vesical neck obstruction due to tumors, diverticula, stones, foreign bodies.

Urethra: obstructions due to stricture and tumor.

Atony of the detrusor muscles of central origin as in *tubes*, multiple sclerosis, myelitis or syringomyelia, or from pernicious anemia, from trauma to the cord or spine, or from tumor of the spinal cord.

Male only: obstructing prostate, benign and malignant, "median bar," sclerosis of the vesical orifice, urethral diverticulum or foreign body, and phimosis.

Female only: cystocele, pressure from a uterine tumor, prolapse of urethra and uterus, and following parturition.

The next patient illustrates strikingly a form of "cystitis" which is quite common and usually undiagnosed except by careful urologic study.

Case III.—Miss D., forty-six years of age, school teacher, entered the hospital two weeks ago because of a marked frequency of urination and suprapubic pain when she attempts to refrain from immediately relieving the urgent desire to urinate which occurs every half hour during the day and every hour during the night.

Her past history is relatively unimportant. Appendectomy twenty years ago; repeated attacks of tonsillitis relieved by tonsillectomy twelve years ago. No gastro-intestinal upsets and is never constipated. For the past twelve years has noted a gradually increasing necessity to urinate at more frequent intervals, this symptom becoming more and more aggravating and with such regularity that "she can almost tell time" by the intervals between voiding. On numerous occasions where she has been obliged to retain the urine after desire to urinate occurred she has had a severe midsuprapubic pain followed by gross hematuria. With the passage of the years she has noted that there has been a smaller quantity of urine voided with each micturition. During the past twelve years she has consulted more than a score of physicians who have examined her and analyzed the urine, and in each instance she was told that the analysis was "absolutely normal." Various medications by mouth were temporarily effective or completely ineffective in prolonging the periods between voiding.

On examination blood pressure was 122/80, blood count normal, and urine shows no albumin, sugar, casts or other abnormal element except for a very occasional leukocyte and erythrocyte in the centrifuged specimen. Cultures obtained after catheterization yielded no growth and special tests for acid-fast bacilli were negative. On cystoscopic examination the bladder capacity was 90 cc. beyond which distention the patient cried out with excruciating pain. There was no stone, tumor or diverticulum seen in the bladder and the ureteral orifices were normal. On the superior lateral walls of the bladder are seen four localized hyperemic areas with dilated capillaries entering them and the center of each of these areas shows a minute ulceration. These involved areas appear sclerotic and inelastic and when the bladder is distended to 100 cc. the mucosa cracks and a tiny spiral of blood circles out of each area.

Diagnosis.—Elusive ulcers (Hunner) of bladder; interstitial cystitis.

Subsequent Treatment.—Spinal anesthesia, overdistention of bladder to 350 cc. by hydrostatic pressure, cystoscopic fulguration of the entire region involved in these four areas.

The general practitioner should be more familiar with the occurrence of *interstitial cystitis*. The lesions initiating this condition are apparently distant foci (perhaps in this patient the tonsils since the bladder symptoms began about the time of their removal) which deposit septic minute emboli in the bladder wall and these areas continue as an active process long after the primary focus has subsided or been removed. These elusive "ulcers," first described by Hunner, are the

initial feature of interstitial cystitis. They may continue in activity or they may eventually heal with such a marked interstitial contracture as to cause a progressive decrease in bladder capacity with resultant marked frequency of urination. The elastic bladder wall is replaced by scar tissue in localized areas and the intravesical distention of these areas causes the cardinal symptoms, *suprapubic pain*, *marked urgency* at times amounting to incontinence, and *hematuria* on overdistention. The *urine is usually clear* and sterile and contains only microscopic blood with rare pus cells. The condition is seen in women twenty times to once in the male. The teeth, tonsils, sinuses, and uterine cervix are said to be the most apparent systemic foci.

Treatment of Cystitis in General.—Relief of cystitis depends on adequate treatment of the causative disease. This frequently requires a complete survey of the urinary tract and allied organs. Palliative treatment in acute cystitis consists of rest in bed, forced fluids, alkalization of the urine and sedatives. Some mixture of codeine and hyoscyamus serves best. Urinary antiseptics are not usually helpful in acute cases because of the dilution of the urine and alkalization. Recently the administration of sulfanilamide in doses of 30 to 40 grains daily for five days and then 15 grains daily for a week has been very effective. This is especially true when the invading organisms are found to be cocci. Local bladder treatment is rarely needed unless there is residual urine. In the latter case interval catheterization or an indwelling catheter may be used and soothing antiseptic irrigations or instillations applied to the bladder cavity.

The treatment and special methods of diagnosis for chronic cystitis are usually the same as for renal infections. Local medication may be used to allay symptoms and hasten cure. Irrigations and instillations of soothing or stimulating solutions are not in vogue as previously but are occasionally effective. Chronic ulcers and localized inflammations of the bladder wall may be treated by cystoscopic fulguration or topical application of solutions of silver nitrate.

CLINIC OF DRS. BEATRICE E. TUCKER AND HARRY B. W. BENARON

THE CHICAGO MATERNITY CENTER

THE MANAGEMENT OF SOME OBSTETRICAL COMPLICATIONS IN THE HOME

THE principles governing the treatment of obstetrical complications are the same whether the patient is cared for at home or in the hospital, but the means of accomplishing the desired results are very different. The physician who works at home is often handicapped by lack of supplies and assistance. However, even with minimal equipment, properly utilized, the patient can be effectively protected against infection, hemorrhage and toxemia. We have found that many difficulties of the environment were overcome in the home service of the Chicago Maternity Center by the application of DeLee's "intensive aseptic technic" to all normal and operative deliveries. This technic is diametrically opposed to the so-called "extensive" technic employed in the hospital.

In the hospital the patient, operating table, and the instrument tables are covered with sterile drapes and sheets. The physician wears a sterile gown and dry sterile gloves. Thus a large area (10 or 20 square feet) is considered surgically clean and a so-called "extensive asepsis" maintained. It is well known that scurf, hair and dust (bacteria) soon settle on this broad expanse of sterile field, and may be easily transported into the wound.

In the home no sterile gown or drapes are used for normal cases and only two sterile towels for operative deliveries. The pans, gloves, instruments and solutions are boiled in the patient's home (Fig. 33). If contamination occurs, and duplicates are not available, it is only necessary to reboil the equipment. The physician wears a clean rubber apron; he

scrubs his hands and forearms and wears boiled wet gloves. The patient is shaved and given a preliminary and sterile

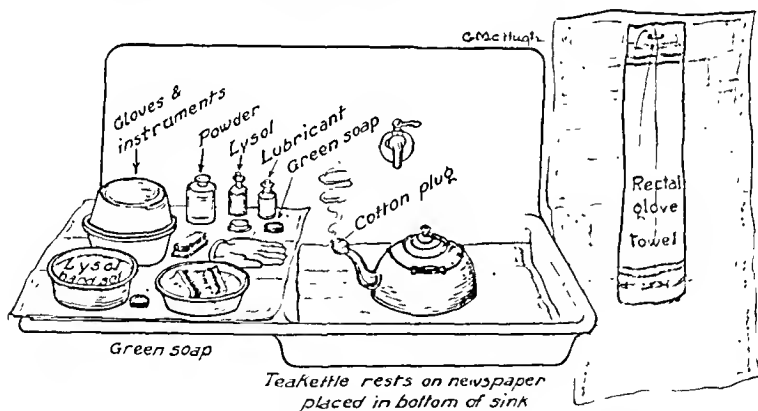


Fig. 33.—The sink board "set-up." The teakettle, solution pans, instruments and gloves have been sterilized by boiling. To facilitate cooling the water, the teakettle is set in cold water in the sink. Following rectal examination the glove is washed in soap and water, lysolized and dried on the rectal glove towel.

preparation. Only the immediate operative field, the doctor's gloved hands, the inside of the pans, the instruments, the solu-

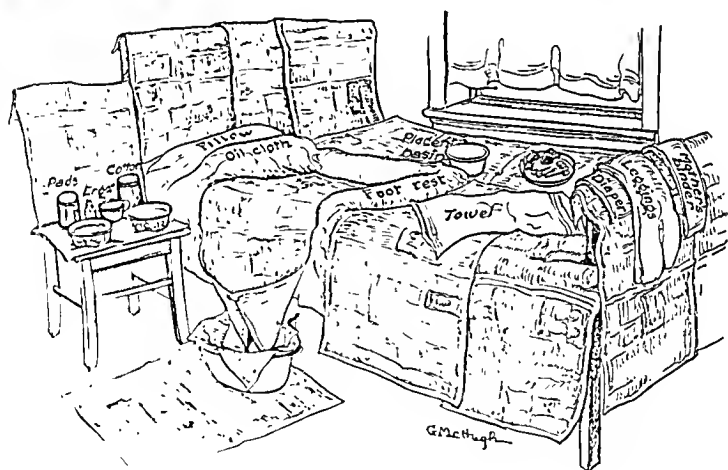


Fig. 34 The bed set-up is used for normal spontaneous delivery and for emergency operative work when no assistance is available. A pakelly pad is made from rolls of newspapers and oil cloth. The patient is delivered lying lengthwise in bed. If operative work is performed with the patient in bed, the rolls are removed, the woman is placed crosswise on the bed and the feet are supported by two chairs.

tions and the pledgets are considered surgically clean. All else is unclean and avoided. Thus, an intensive asepsis is main-

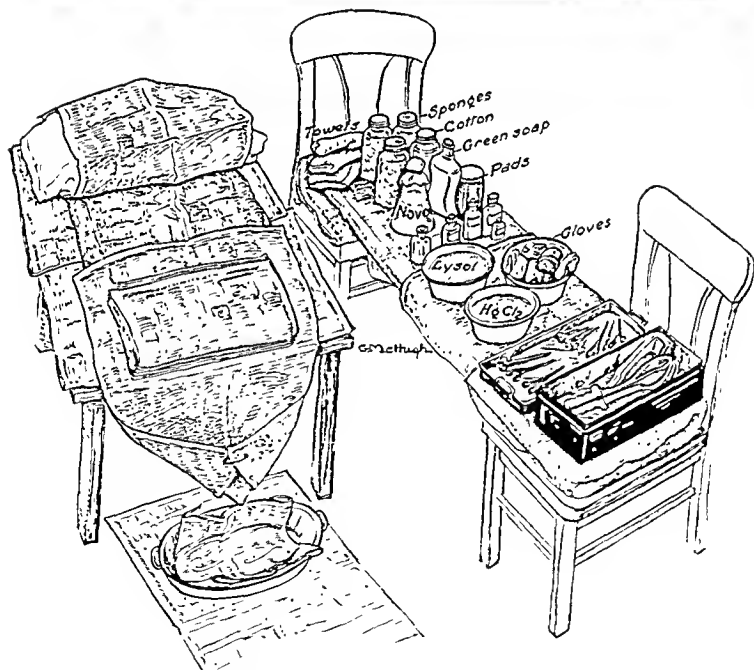
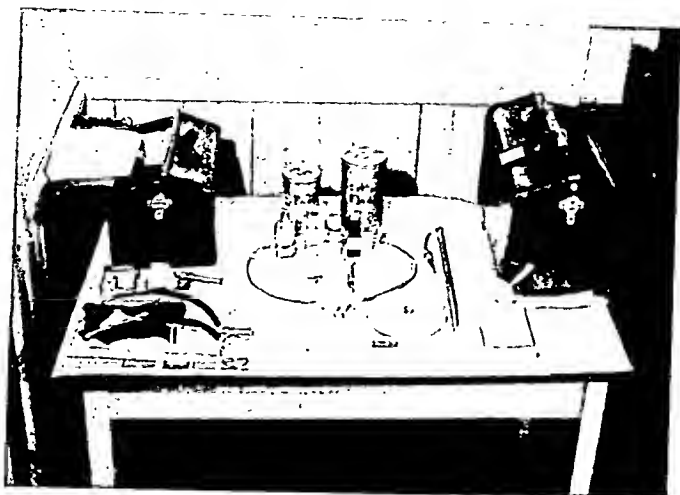


Fig. 35.—The "operative set-up." The kitchen table is padded with blankets and covered with newspapers. This serves as an operating table. The patient is placed upon it in the lithotomy position: the legs are either supported by members of the family or stirrups. We have found those devised by Dr. Russo very useful. An ironing board is covered with newspapers and placed between two chairs. It serves as an instrument table

tained. Normal deliveries are conducted with the patient lying lengthwise in bed (Fig. 34). The patient is placed upon the kitchen table prepared as shown in Fig. 35 for operative work. In this clinic we will consider only some of the obstetric hemorrhages and the treatment described in illustrative cases.

POSTPARTUM HEMORRHAGE

A common and serious complication met in the home is postpartum hemorrhage. Abnormal bleeding following delivery occurred in 4.2 per cent of the women confined on our service. This figure is about 1 per cent higher than the incidence noted by many clinicians. The difference may be attributed to the emphasis placed on blood loss in a home delivery service. We call a slight blood loss a hemorrhage and take alarm at once. Of the 14,156 women delivered from July 1, 1932, to June 30, 1937 inclusive, 2 died of postpartum hemorrhage, 0.014 per cent or 1 hemorrhage death to every 7078 confinements.

Case I.—Confinement No. 13,329, thirty-seven years of age, gravida III, white, registered in the prenatal clinic during the sixth month of pregnancy. There was nothing of note in the past obstetric or medical history. Physical examination revealed an apparently normal gravid woman. The urine and blood pressure were normal, the serology negative, the hemoglobin 85 per cent. Prenatal care to term was adequate and the pregnancy uneventful.

The membranes ruptured prematurely at 8 A. M. on February 22, 1937, the due date. Labor started spontaneously five hours later. The first stage lasted two hours and the pains were intense and frequent. The second stage was delayed because the position was posterior OLP, 145 degrees. At the end of one hour the head rotated anteriorly and ten minutes later an 8-pound 4-ounce baby was delivered.

The third stage was pathologic. Three minutes following delivery there was a flooding and the patient lost what was estimated as 900 cc. of blood. The placenta was partially detached, the corpus high and boggy. Uterine massage and pituitary extract 1 cc. intramuscularly did not control the bleeding. The bladder was empty. An attempt at Credé expression did not deliver the placenta.

The patient was quickly turned crosswise in bed and the feet supported by two chairs. The buttocks were brought well over the edge of the bed. Two fresh pairs of wet sterile gloves were drawn on. Thus the abdomen could be touched with the outer glove without contaminating the inner one. While the right hand supported the uterus abdominally, the left one was introduced into the lower uterine segment. The edge of the placenta was felt with a constriction ring above it. The fingers were introduced into the corpus in the

shape of a cone and overcame the constriction ring by continuous gentle pressure. No anesthesia was used. The placenta, membranes and clots were removed and the lower uterine segment explored for tears. None were found. In spite of uterine massage, the patient continued to bleed. The inner hand grasped the anterior and posterior lips of the cervix and brought them closely together, pushing upward at the same time. The outer hand drew the uterus forward, flexing it over the symphysis (Kumpf). A vibratory massage was given. Oozing continued. Pituitary extract, 3 minims (2 units), were slowly given intravenously and 2 cc. ergonovine intramuscularly. The uterus became very firm and bleeding ceased. The entire blood loss was estimated at 1500 cc.

The general condition of the patient was fair, the color pale, and pulse thready, 130, and blood pressure 70/40. Morphine, $\frac{1}{4}$ grain, and epinephrine, 10 minims (1:1000) per hypodermic, were administered. The foot of the bed was elevated by supporting it with two chairs. Hot-water bottles were placed about the patient and she was wrapped in warm blankets. Five hundred cc. of 20 per cent glucose intravenously and 1000 cc. of normal saline by hypodermoclysis were given. The blood pressure was taken every ten minutes for two hours; it soon rose to 128/72 and was maintained at this level. The pulse dropped to 90.

The patient ran a low-grade fever throughout the puerperium, the highest temperature recorded being 100° F. Temperature was taken twice a day for four days, then once a day. The blood count on the third day showed hemoglobin 60 per cent, red cells 3,500,000 and white cells 11,400. The patient was up and about on the eighteenth postpartum day. The six weeks' examination revealed only an erosion of the cervix.

The management of postpartum hemorrhage in the home taxes the skill, ingenuity and courage of the attendant to the utmost. Much can be done to anticipate or prevent this complication. The history or physical examination may put one on guard, *e. g.*, previous labors, hemophilic tendency, anemia in pregnancy. Careful conduct of the first and second stages leads to a normal third stage. Too rapid labors are slowed up and too long labors are given sedation and supportive treatment. *Pituitary extract and large doses of quinine are never used until after the baby is born.* They are especially dangerous in the home. These drugs not only predispose to ruptured uterus but to deep cervical and fornix tears which may bleed furiously. Credé expression is avoided unless bleeding occurs. Premature efforts to deliver the placenta interfere with the natural mechanism of the third stage and lead to partial detachment and hemorrhage and favor retained secundines.

Postpartum hemorrhage is actively and rapidly treated.

"The blood is the life" is an axiom emphatically kept in mind. Massage, oxytocics and Credé expression may fail. While there is always danger from infection in invading the uterus, the danger from hemorrhage is greater. If the principles of a good, intensive asepsis are observed, there is as little danger from manual removal, intra-uterine exploration and pack in the home as in the hospital.

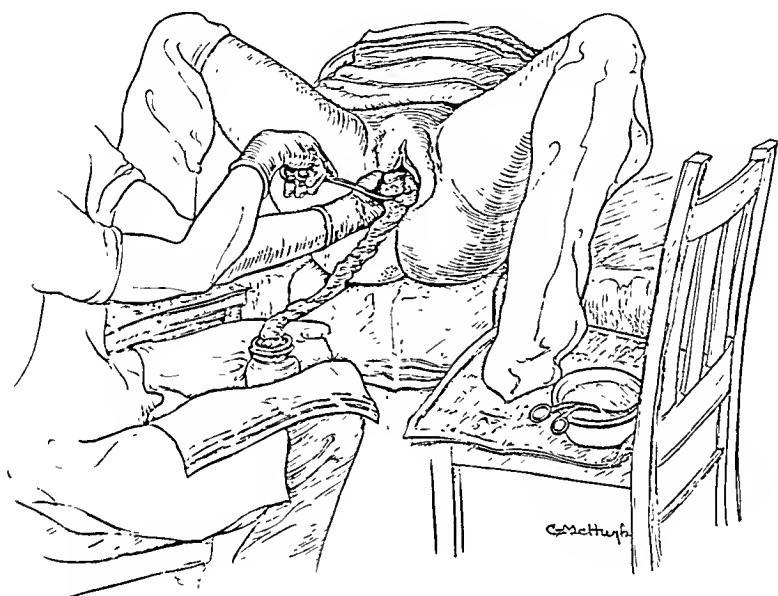


Fig. 36—Technic used for packing the uterus and the vagina in post-partum hemorrhage when no assistance is available. This same method may be used to pack the vagina to control profuse hemorrhage in placenta praevia. The knees of the physician should rest against the buttocks of the patient so that the gauze does not trail. In order not to obstruct the view the doctor is drawn too far back and to one side in this illustration.

If intravenous pituitary extract or ergonovine fails to control bleeding, the placenta having been delivered, the uterus is packed. Wherever possible this operation is performed on the operative set-up (Fig. 35). Where little assistance is at hand, the patient is placed crosswise in bed (Fig. 36). Fresh solutions are quickly made and the hands carefully prepared and gloved. A sterile towel is placed upon the abdomen and one

beneath the buttocks of the patient. The uterus is carefully explored to rule out rupture and to free it of secundines and clots. The physician now sits down in front of the patient on a low stool or box and spreads a sterile towel upon his lap. The sterile packing (12 yards) in a Mason jar is supported between the knees. The doctor's knees covered with the sterile towel should touch the patient's buttocks, which brings the mouth of the jar near the vulva, so that the gauze will not trail. The left hand, palm up, dilates and depresses the introitus. The gauze is packed into the palm with whatever forceps is available. Care is taken that the gauze does not trail or touch the skin. The forceps is put into the lysol solution and the right hand supports the uterus abdominally. The inner hand carries the gauze into the uterus and packs it tightly against the fundus. This procedure is repeated until the uterus and vagina are tightly packed with gauze; from 8 to 12 yards are usually needed.

If no sterile towels or packing gauze are available, the situation need not be hopeless. The uterus is packed with whatever sterile material is at hand, *i. e.*, perineal pads and pledgets. The latter are first wrung out of hot $\frac{1}{2}$ per cent lysol solution. The number used is noted so that when they are removed twelve to twenty-four hours later none will be overlooked. Warning: the uterus and vagina must be tightly packed full and not just a couple of dozen of pledgets used.

If the patient bleeds through the well-packed uterus, one assumes that a rupture of the uterus or laceration has been overlooked, or that a hemorrhagic diathesis exists. One must quickly determine the existence of either. No time is lost in taking the patient to the nearest hospital. *Delay may mean death.* The physician can have his automobile adapted so that it is suitable to carry patients, and he always has room to carry a supply of gauze, prepared solutions, etc.

Part of the routine management of hemorrhage cases is careful inspection of the cervix, vagina, perineum for lacerations. Wherever possible this is done with the patient on the operative set-up (Fig. 35). Repairs are done with local infiltration or pudendal block anesthesia. If the patient has a temperature of 100° F. or over, sutures are only placed to control bleeding. If the temperature is normal, all lacerations

are carefully repaired. Perineorrhaphies are performed using figure-of-8 silkworm gut sutures, and buried catgut is avoided.

The use of intravenous pituitary extract and ergonovine has greatly reduced the necessity for uterine tamponade. In our opinion pituitary extract is a little more dependable than ergonovine. It is not, however, entirely without danger. Reactions do occur and deaths have been reported. The occasional patient has a marked idiosyncrasy. This will be noted following intramuscular injection. Pituitary extract, 3 minims (2 units), given slowly intravenously is followed by very few reactions and the results are excellent. Some men prefer ergonovine (h), $\frac{1}{320}$ grain intravenously.

If a hemophilic tendency is observed, pack with gelatin gauze, give a blood transfusion or inject whole blood into the buttocks.

Supportive Treatment.—While hemorrhage is being controlled, supportive measures to combat shock are often administered. Stop bleeding, but supply previous loss at the same time. Morphine, $\frac{1}{4}$ grain, is given and repeated in four hours if needed for restlessness. Ephedrine, $\frac{3}{8}$ grain by hypodermic or epinephrine, 10 minims (1:1000), may be used to help maintain the blood pressure. The patient is wrapped in blankets which have been warmed in the oven. Hot-water bags, hot bricks or jars of hot water wrapped in towels are placed about her. A supply of blood to the anemic brain is secured by elevating the foot of the bed and resting it on two chairs. If a steeper position is desired, a kitchen chair is turned upside down in bed and padded with pillows. The patient is placed on the inclined back with the head down.

The use of Esmarch-like bandages will conserve the blood volume in the vital centers. These are made by tearing up old sheets or clean clothes into 4-inch strips. The legs are bound from ankle to hip.

It may be necessary to administer intravenous glucose or acacia or to give saline by hypodermoclysis in order to maintain the fluid volume of the circulatory system. Solutions of sterile normal saline, 5 per cent, 10 per cent and 20 per cent glucose and 6 per cent acacia in 500 and 1000 cc. amounts are now put up in sturdy jars which are easy to carry and manipulate. These preparations are stable (Fig. 37). Adapters, rubber

tubing and needles may be boiled on the case or carried sterile. The inverted jar has a bail which is hung on a hook, clothes tree or chandelier. If these solutions are not at hand, an enema can or bag and its tubing may be boiled and a hypodermoclysis needle firmly tied into the distal end of the tubing. Two teaspoonfuls of sterile salt are added to 1 quart of boiled water and this is poured into the sterile enema can and given

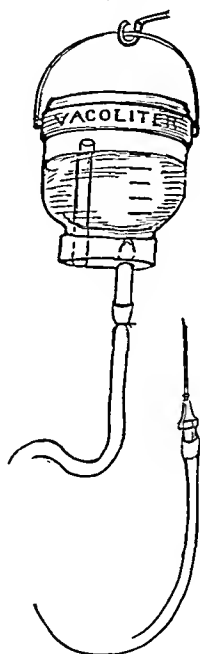


Fig. 37.—Five, 10 and 20 per cent glucose, normal saline, and 6 per cent acacia, are now commercially available in sturdy containers. The solutions are sterile, stable and furnish a convenient, inexpensive means for the administration of parenteral fluids. Rubber tubing, adapters and needles are sterilized by boiling.

subcutaneously into the inner aspect of the thighs, not under the breasts.

Blood Transfusion.—The actual administration of citrated blood is a simple procedure in the home. However, the equipment necessary for matching and running the Kahn test is too elaborate to be practical. In some communities where hospitals are not available the physician needs to have at his

command a list of registered donors and complete facilities for cross typing and administering blood. If there is a secondary fall in blood pressure after the intravenous administration of fluids, blood transfusion is essential in order to save the life of the patient. Six per cent acacia intravenously is very effective where blood cannot be obtained, but it must be used cautiously since Studdiford reported 2 deaths from it.

RETENTION OF THE PLACENTA

Retention of the placenta may require operative interference. Three hundred and forty-eight women had placentae

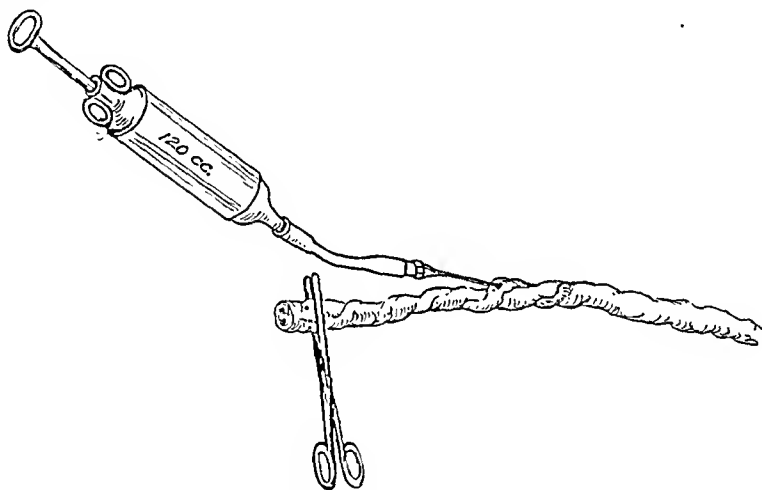


Fig. 38.—Gabaston technic for separating and delivering the retained placenta: 150 cc. of sterile normal saline are injected into an umbilical vessel. Any syringe may be used but we have found a 120-cc. all-metal Alexander syringe most satisfactory, a rubber adapter and an 18- to 20-gauge needle necessary.

retained one hour or longer in the last 14,156 confinements, an incidence of 1 to every 42 deliveries; 15.2 per cent of the 348 women required operative interference, 48 manual removal, and 5 injection of the umbilical cord with normal saline as described by Gabaston (Fig. 38). This latter method is tried in septic or potentially infected cases to avoid invading the birth canal. In addition to the above cases, manual removal was performed eighty-two times for hemorrhage. One of these patients had

had an operative delivery under ether and died on the ninth postpartum day from pneumonia. One postpartum hemorrhage patient who died had had a manual removal of the placenta one hour before death.

Case II.—Mrs. T., twenty-seven years of age, colored, gravida VI, had delivered spontaneously 4 full-term babies and 1 abortion. A diagnosis of a three months' pregnancy was made in clinic on November 25, 1935. The patient was not desirous of another child. On January 20, 1936, an abortion was self-induced by digital dilatation of the cervix and rupture of the membranes with the fingernail, and she delivered, unattended, a five months' fetus. Three hours later the placenta had not come and she called for help. There was very little blood loss. The temperature was 101° F., pulse 120. Pituitary extract, 1 cc. did not separate the placenta. The patient was prepared for operative interference; 150 cc. of sterile normal saline was injected into an umbilical vessel as shown in Fig. 37. The placenta detached immediately and was delivered by expression. The puerperium was uneventful. The six weeks' examination in clinic revealed a subinvolved uterus and a low-grade left parametritis; temperature 98.6° F. and pulse 80.

PLACENTA PRAEVIA AND ABRUPTIO PLACENTAE

Placenta praevia and abruptio placentae are ominous conditions to care for in the home. Antepartum bleeding in the last trimester of pregnancy occurred 140 times in the 14,156 women delivered at home, and 232 times in the 636 women who were hospitalized from our service. Usually no attempt is made to establish a diagnosis at home because, if a placenta praevia is present, rectal or vaginal examination may cause a severe or even fatal hemorrhage. The women who were delivered at home either refused hospitalization or else their labors were rapid and far advanced. None of these had placenta praevia centralis. No patient died from antepartum bleeding.

Case III.—Patient, eighteen years of age, gravida I, unregistered, first called the Center March 29, 1934, during the thirty-eighth week of her pregnancy because of vaginal bleeding. The patient was seen immediately. She stated that when she went to the toilet she had lost "a cup of blood." She had no pain. Upon examination there was a small trickle of blood running from the vagina. The uterus was about the size of a thirty-eight-week pregnancy, soft and not tender. The fetal heart tones were 120, position and presentation OLA, head floating, membranes intact. The blood pressure was 126/60, temperature 98.6 F., pulse 92. A rectal examination was inadvisedly made and the patient began to bleed furiously. She was quickly shaved, prepared and placed crosswise in the bed (Fig. 36). Sterile vaginal examination revealed a placenta

prævia centralis. The vagina was tightly packed with 5 yards of uterine packing gauze (Fig. 36). This controlled the bleeding. A tight binder was adjusted to the abdomen. She lost what was estimated as 800 cc. of blood. The patient was transported to the hospital by ambulance with members of the family who might act as donors. At the hospital the woman was transfused and a laparotrachelotomy performed. She ran a low-grade fever of 99° to 101° F. throughout the puerperium and was discharged with the baby on the fourteenth postpartum day, afebrile and in good condition. The six weeks' examination revealed a firm scar, the uterus was anterior and freely movable.

Severe hemorrhage in placenta prævia may be controlled by packing the fornices and vagina tightly with gauze or wet pledgets, using the technic described above and illustrated in Fig. 34. From 6 to 8 yards of packing or a large jar full of pledgets are used. The vagina is packed until it bulges and then the introitus may be sewed shut with a couple of silk-worm gut sutures to assure counterpressure. A tight binder is adjusted on the belly. This type of treatment will control bleeding while the patient is transported to the hospital. We have found packing safer than trying to attempt Braxton-Hicks version or intra-ovular bag insertion in the home, unless blood transfusion facilities are at hand. If a good technic has been observed, even laparotrachelotomy may be performed later in a good hospital, if it is indicated, without fear of infection.

Since our experience with the above patient, we never make rectal examinations on antepartum bleeding cases. If the diagnosis must be established at home, we prepare the operative set-up, shave and prepare the patient. Voorhees bags are boiled up ready to insert. Packing and version slings are ready. A careful vaginal examination is made. If severe hemorrhage results, it can be controlled by packing, as described above, the insertion of an intra-ovular bag or by Braxton-Hicks version. If a version is performed, the entire set-up is kept sterile and the doctor remains scrubbed up until the patient is safely delivered, even though it be twenty-four hours or longer. Labor should be slow and all oxytocics are contraindicated. The baby is never extracted but allowed to deliver spontaneously. Fatal hemorrhage may follow the tiniest laceration to the cervix or lower uterine segment. It was only necessary to pack 2 of the 232 women who were hos-

pitalized for antepartum bleeding during the last trimester of pregnancy. In both cases inadvised examinations had been made.

Case IV.—Patient, twenty-nine years of age, colored, gravida VI, reported in clinic February 18, 1936, three months pregnant. Her past obstetric and medical history were essentially normal. Examination revealed an apparently normal gravid multipara with blood pressure of 110/60, urine and serology negative, hemoglobin 90 per cent. From February 18 until April 26, 1936, she made 4 visits to the clinic and the findings were normal. On July 19th, three months later, she called the Center because of vaginal bleeding. This was one month from her due date. She was found lying in bed in a pool of blood. She had had no pain but at 10 A. M., one hour before the doctor's arrival, she had lost about "a pint of blood." She did not correlate this with any trauma or exertion. The blood pressure was 162/110, pulse 90, temperature 98.6° F. A clean specimen of urine was boiled in a tablespoon and 3 drops of vinegar added; 2 + albumin was present. Abdominal examination of the patient showed the uterus to be the size of a full-term pregnancy, although she was one month from term. The organ was rigid and tender. No fetal parts could be identified and no fetal heart tones heard. A diagnosis of complete abruptio placentae and toxemia of pregnancy was made and hospitalization urged. The patient refused. Sterile vaginal examination revealed a multiparous, gaping introitus; the membranes were intact; no placental tissue was palpable; the cervix was soft, uneffaced, 2 cm. dilated; position and presentation OLP, fetal head floating; the pelvis was normal. The membranes were ruptured artificially and a few old blood clots escaped with the amniotic fluid. A Voorhees bag No. 9 was inserted into the cervix, filled, and a milk bottle half full of water was attached to a tape and tied to the stem of the bag (weight, 1½ pounds). Quinine, 3 grains, was given every fifteen minutes. Weak pains started within one hour. The blood pressure remained high but the pulse increased to 138. Pituitary extract, 1 minim, per hypodermic was given every fifteen minutes for 3 doses. *The only indication we have for the use of pituitary before the birth of the child is abruptio placentae.* Two hours after the insertion of the bag, labor was definitely started. The blood pressure varied from 162/112 to 182/126, the pulse from 112 to 138, and was of good quality. At the end of four hours the cervix was 6 cm. dilated, the pulse rate increased to 152, the blood pressure fell to 126/90. Beads of perspiration stood out on the patient's face. The bag was removed and the cervix manually dilated to 8 cm. The anterior sacral nerves were blocked with 150 cc. of ½ per cent procaine-epinephrine solution (parasacral anesthesia). A craniotomy was performed. Following the extraction of the baby the placenta was found in the cervix completely separated. What was estimated at 1000 cc. of old blood clots immediately followed. The uterus was explored and found intact. Pituitary, 3 minims (2 units), intravenously and gynergen 1 cc. intramuscularly were given. The uterus immediately became firm and remained so. The pulse following delivery was 156 and the blood pressure 120/60. Five hundred cc of 20 per cent glucose were administered intravenously, also 1000 cc. of normal

saline by hypodermoclysis and morphine, $\frac{1}{4}$ grain, by hypodermic. The baby weighed $5\frac{1}{2}$ pounds. Two hours following delivery the blood pressure rose to 156/100 and the pulse was 126. On examination the placenta showed a large retroplacental hemorrhage with excavation of almost the entire maternal surface; a fetus papyraceous the size of a three months' pregnancy was in the secundines. The puerperium was afebrile, the blood pressure remained high.

The cases presented have demonstrated the management of some serious obstetrical complications in the home. Where good hospitals are available, the physician usually elects to take advantage of their facilities. Many communities do not have good hospitals for the obstetrical patient. The physician who has mastered the intensive aseptic technic can, with minimal equipment and assistance, skilfully apply the principles of good obstetrical care to the patient in her own home and either terminate the case there or safely transport her, when necessary, to a good hospital, even though the distance may seem prohibitive.

The necessary equipment for normal and operative deliveries is listed below:

Necessary Equipment for Normal Delivery:

- | | |
|---|--|
| 2 6-inch clamps | 1 vial of sterile salt, 8 Gm. (for hypodermoclysis) |
| 1 scissors | 1 sterile douche can with tubing |
| 1 pelvimeter | 2 sterile brushes |
| 1 head stethoscope | 2 boxes sterile green soap |
| 1 rubber catheter | 2 cans sterile cotton pledgets |
| 1 tracheal catheter | 2 cans sterile perineal pads with 2 cord dressings |
| 1 Baumanometer | 2 vials sterile cord tape |
| 1 set of records | 1 2-cc. hypodermic syringe |
| 2 1500-cc. basins | 1 subcutaneous, intravenous and |
| 2 1000-cc. basins | 1 hypodermoclysis needle |
| 1 500-cc. basin | 2 ounces 70 per cent alcohol |
| 1 rubber apron, cap and mouth piece | 2 ounces lysol |
| 2 pairs good rubber gloves in hoiling bag | 50 bichloride tablets |
| 1 old pair rubber gloves (for rectal examination) | Medication: |
| 1 razor with new blade | 1 vial paraffin ampulets of 1 per cent silver nitrate |
| 1 tube sterile lubricant | Sterile ampules of pituitrin, ergonovine, coramine and epinephrine |
| 1 bottle talcum powder | 1 vial morphine, $\frac{1}{4}$ grain |
| 1 pair clean leggings | 6 capsules quinine sulfate, 3 grains |
| 1 padded clothes pin (for possible eclampsia) | 1 vial ergotrate tablets, $\frac{1}{320}$ grain |

Additional Equipment for Operative Delivery:

- 2 jars sterile antiseptic uterine packing gauze (1 12 yards and 1 8 yards)
- 2 jars sterile cotton pledgets
- 3 jars sterile perineorrhaphy sponges
- 8 sterile towels
- 4 pairs good rubber gloves (2 long, 2 short)
- 3 cans ether, mask, airway and vaselin
- 12 tubes of sterile chromicized catgut (No. 1 and 2)
- 1 glass screw cap bottle of sterile silkworm gut suture in 1:500 bichloride
- 1 vial soda bicarbonate for boiling instruments
- 1 vial novocain tablets
- 1 vial of sterile salt, 8 Gm., for hypodermoclysis
- 1 10-cc. Luer syringe with fine needle, 8-cm., 10-cm. and 15-cm. needle for administering local infiltration, pudendal block and parasacral anesthesia
- 4 ounces sterile green soap for lubricating vagina

Instruments:

- 1 sac containing a set of Voorhees bags, all sizes, and a syringe for filling
- 1 De Lee obstetrical forceps (long shank)
- 2 needle holders (1 long)
- 2 scissors (1 long)
- 2 double vulsellum forceps
- 7 6-inch hemostats
- 3 retractors, various sizes
- 1 lifting forceps
- 1 uterine packing forceps
- 2 tissue forceps (1 long)
- 1 scalpel
- 2 8-inch hemostats
- 5 Allis forceps
- 2 ring forceps
- 1 instrument pan with cover
- 1 embryotomy set comprising Zweifel De Lee cranioclast, perforator, trephine, Seibold scissors, Braun's decapitator, bone forceps and blunt hook
- 1 500-cc. vacoliter 20 per cent glucose
- 1 500-cc. vacoliter of 6 per cent gum acacia
- Sterile adapters, tubing and intravenous needles

CLINIC OF DR. N. SPROAT HEANEY

PRESBYTERIAN HOSPITAL

DIAGNOSTIC ERRORS IN EXTRA-UTERINE PREGNANCY

I HAVE a very interesting case to present this morning. This patient is a young single woman sent to us for the removal of her appendix because of right-sided pain associated with a leukocytosis of 18,000. This young woman of twenty-six has always been perfectly well and sturdy until the onset of the present difficulty yesterday early. While at stool after breakfast she had a rather sharp pain in the right side, transitory in nature, which, though short in duration, left her exhausted. The bowel movement was formed and was accompanied by no unusual amount of gas. The patient had a formed bowel movement again this morning so we can rule out bowel colic as the cause of her pain rather certainly. At noon yesterday after eating heartily she had another seizure of pain of similar character somewhat sharper but also short in duration. Early this morning a third attack of pain occurred still more intense and at that time she called a physician who found her tender over the region of the appendix. He made a leukocyte count and found it 18,000 while her temperature and pulse were normal.

Now, this patient is before us and not one word has been said by her attending physician nor by the intern, who took her history, about her menstrual periods. How many errors in medicine are attributable to that lapse. I want to tell you that you will be wise to take a menstrual history on every woman you are called upon to treat. It may be thought that a brain tumor is present and is producing vomiting until a menstrual history with subsequent examination shows that the vomiting is due to an ordinary common everyday pregnancy.

You may be a skin man treating a case of baffling urticaria until a menstrual history shows that the patient is pregnant and the urticaria is toxic in origin. When we question this patient about her menses she states that she has been always regular every twenty-eight days and that her last menstrual period was ten days ago and on time.

If you want to avoid frequent and important errors in gynecologic diagnosis you must not take a statement to the effect that the last period was on time and normal in every way, without a bit of doubt. Every woman will stand a little cross examination on this point. First of all, if a woman really menstruates every twenty-eight days on the dot then she must necessarily begin menstruating each time on the same day of the week. Occasionally a woman is that regular, but most are not. This woman says that she does not always begin to menstruate on the same day of the week so immediately we know that her last menstrual period's regularity is questionable; it may have been a few days late without attracting her attention. She states that the period was normal but when we examine into details she says that while she normally menstruates always for four or five days and uses 10 to 12 pads that this time she "menstruated" very scantily for three days then stopped entirely for a day or two and then began spotting, and that this spotting has continued until now.

Gentlemen, this is a very suspicious symptom in a woman complaining of "appendicitis." When I asked this patient if there were any chance of her being pregnant she was indignant at the suggestion. This proves nothing, however. If she had said there was, it would have been contributing testimony; her denial means nothing. Last week I saw a girl close to term where the fetal parts could be mapped out and where you could hear the unmistakable fetal heart and could see the baby lunge about and yet she insisted that I was in error. So we will not allow the history in this regard to influence us.

So we will proceed to our examination to prove that this patient who has been regular all her life, menstruating each month for five days and each time freely, and for a like amount each month, but who ten days ago had an abnormal period, is not pregnant. My belief is that she is, for any woman who has a scanty "period" and then spots on and off for ten days

afterward is probably pregnant. Had she bled profusely for the last ten days the same suspicion would hold, particularly if we could elicit the fact that she had gone over her last menstrual period a few days or a week before this abnormal bleeding began. Were the patient married we would be less suspicious of a basis for deception, although there might well be, even then, a reason why the patient might deny the possibility of pregnancy.

We will examine her, but what findings can there be this early in pregnancy to guide us? Can you find enough enlargement in a uterus of an unknown patient ten days after the expected period to make a diagnosis? Rarely. If then it is an ectopic pregnancy would you be able to feel an enlargement of the tube? You would not. Then why examine her if you can anticipate no findings. Well, we'll do it anyway, maybe we will find something, who knows? The vagina easily admits 2 fingers without discomfort. That's one finding. The cervix is small—not softened, and the body of the uterus is smaller than normal, so small that one could be almost certain that it holds no pregnancy. We will now palpate the region of the tubes and ovaries. I can feel the left ovary as normal, on the right side I feel nothing but I elicit a lot of tenderness. We will make a rectovaginal examination as should be done in every case examined for the first time for the rectal finger can go higher than the vaginal vault and frequently picks up findings missed by vaginal examination. No—we find nothing in the appendages. We found no swelling of the ovary so we are not dealing with a torsion of an ovarian cyst which gives a similar picture of acute pain associated with a leukocytosis, and no temperature until the torsion has existed so long that gangrene of the cyst occurs. Nor is there a corpus luteum cyst which in early pregnancy is frequently mistaken for appendicitis or for an ectopic pregnancy.

Let us now review our history and our findings. We have a young lady with roomy vagina who ten days ago had what she called a period but the bleeding was scanty, of short duration and reappeared at irregular intervals as spotting up until the present time—this is very suspicious of pregnancy. She has a leukocytosis of 18,000. If the leukocytosis were due to appendicitis then the appendix would be acutely inflamed and

we would have elevated temperature, which we have not, therefore we have no appendicitis. A catheterized specimen of urine is free of pus and red cells which excludes a ureteral attack. We have no swellings, which excludes inflammation and torsion and corpus luteum cyst. We have a patient whose last normal period was about five and one-half weeks ago, who has had abnormal bleeding with seizures of severe pain with leukocytosis. The leukocytosis is higher than we get in early pregnancy; it could be due to hemorrhage into the abdominal cavity in an amount insufficient to produce shock but sufficient to produce a leukocytosis. You are well acquainted with the fact that hemorrhage into the abdomen may produce a marked leukocytosis. We said that the uterus is so small that its very size almost precludes the probability of an ovum being in it. We believe the patient is pregnant, if it is not in the uterus then it must be in the appendage. And remember that one of the causes of ectopic pregnancy is undeveloped tubes. When the tube is very small its lumen may be too small to allow the egg to pass so it lodges and embeds itself. There is no way of determining that this patient's tubes are small, yet if her uterus is very small her tubes are probably proportionately small. Be on your guard for ectopic pregnancy when in the presence of pregnancy symptoms you find a tiny uterus.

Now, what will we do in this case? We have a young woman where we suspect an ectopic pregnancy yet she is not ill enough to justify a laparotomy particularly in the absence of pelvic findings. Nausea, abnormal cravings, enlargement of the breasts, and colostrum what of them? We would not expect to find them this early in a normal pregnancy—their absence in this case means nothing. An Aschheim-Zondek test we have started. What if it is negative? We know that at this early stage it is frequently negative when later the patient proves to be pregnant and reacts positively.

What will we do with this case? Put her back to bed on observation? To watch her for what? Enlargement of the pregnant tube? If she has an ectopic pregnancy this pain, transitory faintness and leukocytosis means that she has had a partial rupture or a partial tubal abortion. How long will it take for the tube to get big enough to palpate? So long that the patient will probably have a complete rupture before

that time comes. Most tubes rupture before they ever get big enough to feel. In this clinic we do not put suspected ectopic pregnancies to bed for observation. The history here is that of an early disturbed pregnancy, that is reasonably certain, either a disturbed uterine pregnancy or an ectopic. The abnormally small uterus, the typical pain and the leukocytosis make it very suspicious of an ectopic pregnancy.

I am not going to put this patient back to bed on observation—I have had her prepared both abdominally and vaginally for operation and, first of all, I am going to dilate and curette the uterus for if it is a uterine pregnancy it is disturbed and not worth saving anyway.

The cervix dilates like a nonpregnant uterus. Gently curetting I get no scrapings. Now the good textbooks tell us that if the scrapings from a pregnant woman are examined villi will be found when the pregnancy is uterine, and no villi will be found if an ectopic pregnancy is present. That sounds very simple. If villi are found there can be no question of the pregnancy being uterine for villi are fetal in origin. When, however, you find no villi in uterine scrapings you cannot say that there is no uterine pregnancy present unless the uterus has been thoroughly emptied and unless all the scrapings obtained have been thoroughly examined. The curettings obtained in an early pregnancy may be scraped from an area too far from the embedding place of the ovum to show villi and consequently the tissue in the sections may not contain villi. One must save all the tissue obtained and all tissue must be examined thoroughly before the absence of villi can be held of any importance. The textbooks do not tell you what to do if you get no scrapings. No uterine pregnancy ever aborts so completely that if you curette the uterus while the patient is still bleeding you will not get abundant scrapings. The fewer the scrapings obtained the more probable the ectopic pregnancy. If you get a dry scrape an ectopic pregnancy is almost certain. Now remember that fact. If you curette a case of what you have thought to be a threatened or incomplete abortion and you get a dry scrape it is not because you got there too late, it is because you are probably dealing with an ectopic pregnancy. Quite true that the endometrium undergoes a decidual reaction and thickens in ectopic pregnancy and that

if you examine the scrapings you get typical decidual reaction, that is, if you get any scrapings. By the time most ectopic pregnancies get to the operating table the uterus has expelled all the decidua and you get a dry scrape. Now what will I do? I have a patient in whom I have diagnosed a pregnancy stating that it is either an early disturbed uterine pregnancy or an ectopic pregnancy. Curettage gave us no scrapings—it is therefore not a uterine pregnancy but an ectopic pregnancy. Shall I put her flat and go into the abdomen by a midline incision? I think not—I should like a little more certainty that there really is an ectopic pregnancy. I am a little too cagey when symptoms are no more outspoken than these to plump myself into a laparotomy. Looking back over a considerable period of years I can remember visiting clinics a good many times where, under exactly similar conditions, the diagnosis of an ectopic pregnancy has been made and a laparotomy has been performed with dispatch and certainty and no ectopic pregnancy has been found. One of you suggests that I use an aspirating needle to see if I get blood in the cul-de-sac. What am I going to aspirate? I have no swellings to stick and it is dangerous to shove a needle through the fornix hoping that I will land by a stroke of luck in a pool of blood. When you have a definite swelling and fluctuation is undoubtedly present I have no objection to using a large caliber aspirating needle under the guidance of a finger in the rectum to see whether fluid may be obtained. If I get fluid I have gone a step forward in diagnosis. However, it is not at all exceptional that when I am dead certain that I have an abscess in the cul-de-sac or a hematoma in the broad ligament I fail to get anything upon aspiration because the substance is too thick to pass through the needle. I have in mind many cases where aspiration failed to show pus, yet puncture with a pair of sharp scissors yielded abundant pus. However, aspirating a mass is one thing and trying to strike free blood in the cul-de-sac is another.

Palpation here shows a roomy nulliparous vagina, a freely movable uterus and a roomy cul-de-sac. I am going to make a colpotomy incision and see if an ectopic pregnancy is present. I pull the cervix well down with a bullet forceps and then strongly forward toward the symphysis. With a tissue forceps

I pick up the vaginal mucous membrane in the fornix. Just posterior to where the mucosa is attached to the body of the cervix I make a transverse incision about 1 inch wide. I take care not to open the cul-de-sac at one fell swoop—I may enter the rectum instead. Now I push the posterior edge of the incised mucous membrane backward $\frac{1}{2}$ inch or so and I see now the thin peritoneum showing through. Frequently, if considerable blood is present in the cul-de-sac, particularly if it has been there for some time, this bulging peritoneum will be bluish or greenish. Here there is no discoloration. There is a tiny spurter underneath the mucosa here which I will tie off because I want the wound to be dry the moment I incise the peritoneum. If there is any blood in the cul-de-sac I want to be certain whether it came from the peritoneal cavity or from my incision. I now incise the peritoneum and look quickly and there escapes through the incision a teaspoonful or more of bright blood. It is almost a certainty that I am dealing with an ectopic pregnancy. Occasionally a ruptured corpus luteum will give free bleeding. Had I got no blood I would, nevertheless, have introduced a pair of narrow-bladed L-shaped special vaginal retractors, put the patient in somewhat elevated lithotomy position and looked at the ovaries and tubes. Had I found no ectopic pregnancy I would have sewn the incision up with 3 or 4 interrupted chromic catgut sutures and the patient would have been no worse off than with the curettage alone and would have had to stay no longer in the hospital nor would she ordinarily have been any sicker than after a simple curettage.

I have, however, found free blood and I can either search further to see just where the pregnancy is or I can close the incision, put the patient flat and enter the abdomen with every certainty that I am not performing a laparotomy with all its potential possibilities unnecessarily. Making a colpotomy incision is a triviality by comparison. One of you states that having entered the pelvis by colpotomy you would hesitate now to go in from above because of contamination. How do you mean contamination? This vagina was very thoroughly scrubbed, the cervix was free of infection and after the curettage the uterine cavity was swabbed out with iodine and the vagina was very thoroughly iodized. Some of you cer-

tainly have peculiar ideas, likening the vagina to a cesspool. Where do you get that way! Get over your timidity regarding the danger of an exploratory colpotomy. I think it is one of the most important technics that a gynecologist can have at his disposal and I am certain that if all gynecologists familiarized themselves with it they would save their patients many unnecessary laparotomies. Afraid to go into the abdomen from above after simple colpotomy! What will you say when I state that very frequently in complete hysterectomies, for one reason or another, for example a badly infected cervix with a low, broad fibroid pressing against the rectum, I remove the cervix from below after opening both anterior and posterior cul-de-sacs and, then after closing the vaginal vault, that I enter the abdomen by laparotomy for the removal of the rest of the uterus. Yes, and frequently to the patient's great benefit. Never have I seen anything in the postoperative course of such a patient to make me think that I had contaminated the pelvis in any way.

This pregnancy is a very early one and the patient is not bleeding freely so my vision will probably not be interfered with so I think I will see if I am able to remove this pregnancy through the vagina. With the narrow-bladed retractors still in place I widen the incision from the sacro-uterine ligament on one side to the opposite one. I now place a bullet forceps transversely through the cervix just anterior to the incision and pull rather strongly downward and forward toward the symphysis—this tends to make the uterine body rotate posteriorly. I now remove the anterior retractor and with a bullet forceps reach through the incision and under the guidance of the eye take a hold on the posterior wall of the uterus. Now the bullet forceps is removed from the cervix and the one on the posterior wall of the uterus is pulled so as to draw the body of the uterus toward the incision. As the uterine body presents itself other bites are taken until either the body is delivered into the vagina or the right uterine horn is thoroughly exposed. The fixed portion of the tube is now visible and the remainder of the tube is gently drawn into the incision by tissue forceps. Here in the distal third we see a bluish swelling of the tube the length and thickness of the distal phalanx of my little finger—there is our ectopic preg-

nancy! Who of you is so clever that you can palpate a pregnancy of that size by vaginal examination? There is no rupture present but you see blood freely oozing from the tubal ostium. I ligate the blood supply of the distal portion of the tube and loosen the tube from its mesentery. I now excise the rest of the tube from the uterus and pick up all bleeding vessels with a running suture. The opposite tube and ovary are now searched for, are found and look normal. The uterus is now released, the body pushed back into the pelvis and the incision closed with through-and-through interrupted No. 2 ten-day chromic catgut after having wiped the cul-de-sac free of blood. This operation was successfully completed by the vaginal route but I would have deserted this route at any moment that I thought my difficulties could be more readily solved by laparotomy, for the abdomen was prepared for that possibility before we did the curettage.

This patient will be kept in bed one week and, barring the unexpected, will be able to leave the hospital on the tenth day. I confidently predict that she will eat and retain all her meals tomorrow and will have a far easier convalescence than if I had entered her abdomen from above.

I am not advising you to try to operate your ectopic cases by the vaginal route. I am, however, telling you that when the diagnosis lies between a clean, incomplete or imminent abortion and ectopic pregnancy to curette the uterus on the basis that persistent bleeding indicates a pregnancy not worth saving and that if you get a dry scrape to change the diagnosis to ectopic pregnancy. I am also advising you that where the symptoms are no more pronounced than they were in this case to save yourself the embarrassment of a mistaken diagnosis and the patient the danger of an unnecessary laparotomy by doing an exploratory colpotomy for diagnostic purposes.

This case teaches a homely everyday fact which those who treat women should always bear in mind—the usual and ordinary cause of a single abnormal so-called “menstrual period” is pregnancy.

CLINIC OF DR. SIDNEY A. PORTIS

COOK COUNTY HOSPITAL

ACIDOSIS AND ALKALOSIS

No more interesting phase of medicine has intrigued the physician than changes in the acid-base equilibrium of the body. This morning I should like to discuss various phases associated with these changes, their symptoms, complications and management. It is not the purpose of this clinic to discuss diabetic states, as they have been discussed elsewhere.

One of the most common conditions in which alkalosis is found is the result of overalkalization in the treatment of peptic ulcer. Many physicians, having no conception of the vulnerability of the acid-base equilibrium, indiscriminately give alkalis to patients in order that symptoms may be relieved, and the subsequent train of symptoms that supervenes is frequently interpreted as the result of dietary indiscretion or the patient's becoming dissatisfied with his strict diet. Many patients on ulcer management complain of an early slight nausea, which is frequently overlooked by the physician, and later develop some vomiting. The physician, thinking that this condition might be associated with some pylorospasm, continues to prescribe alkalis for the patient, who then develops the beginning of a very definite trend of symptoms, ushered in by nausea associated with headache and followed by vomiting; as this trend of symptoms increases, vertigo becomes evident. A marked anorexia is present from the onset. If the vicious circle is not interrupted, more severe symptoms ensue.

What is this vicious circle? When a patient loses hydrochloric acid there is a definite loss of blood chlorides, which is a common finding in alkalosis. Along with this loss of blood chlorides there is also a loss of the hydrogen ion. The loss of

these two combined gives rise to an increased carbon dioxide combining power and content of the blood. Therefore, in the administration of alkalis to a patient already in a state of beginning alkalosis, the physician merely aggravates the picture. As the vicious circle ensues and remains unrecognized by the physician, an edema of the subcutaneous tissues takes place; the urine output is lessened, and, if allowed to go unrecognized, patients begin to show a giddy delirium, which for all intents and purposes cannot be differentiated from an alcoholic delirium. During this time the pulse is not greatly accelerated; the blood pressure may be increased; the urine is definitely alkaline, containing a large amount of serum-albumin and, as a rule, no red cells are present. The chemistry of the blood shows a carbon dioxide content and combining power elevated; the pH of the blood raised, the chlorides depleted, the non-protein nitrogen elevated and the serum-albumin ratio modified and in some instances may approach even a 1:1 ratio. Unfortunately, when patients reach this extreme state, therapeutic approach to the problem is almost hopeless. I do not need to cite cases to bear out the statement that alkalosis is common in ulcer management, for it would be merely a repetition of some of the previous clinical presentations.

I mentioned before that vomiting produces an alkalosis. Therefore, in all cases of vomiting, if persistent with loss of gastric secretion, alkalosis might develop. This is a frequent postoperative complication; particularly is it true of upper abdominal operative interference. For instance, the so-called "postoperative dilatation of the stomach," sometimes called gastric tetany, emphasizes the conception that alkalosis may be a factor in this unfortunate clinical picture. However, I do not believe that the stomach *per se* is responsible for this condition, as my clinical experience leads me to believe that gastric dilatation following operative interference is the result of neuromuscular involvement of the second and third portions of the duodenum. This marked duodenal ileus is responsible for a reflex aperistaltic stomach, which as part of its clinical picture continues to fill up more and more as it relaxes. The increased size and weight of the stomach becomes an additional factor in interfering through its pressure on the emptying of the retroperitoneal portion of the duodenum and therefore

tends to increase the duodenal ileus. This is an exaggerated picture of duodenal ileus. Duodenal ileus exists in milder states. For instance, the symptoms that are associated with visceroptosis, particularly gastropptosis, are not caused by a lowered position of the stomach in itself but result from the temporary delay of a mild to a marked degree in the second and third portions of the duodenum. This is no theoretic consideration because laboratory data support this fact to a degree depending on the severity of the pathology and symptoms. So is it any wonder that these asthenic individuals with marked gastropptosis complain of anorexia and occasional nausea, headache, vertigo and loss of weight? Parenthetically it might be added that many of these persons are treated as incipient tuberculous patients, only to find that no definite evidence of active tuberculosis exists. They complain of many functional nervous manifestations, and may it not be that changes in the acid-base equilibrium of the body are responsible for disturbed cerebral function?

In my discussion some time ago regarding the symptoms of gallbladder disease I called particular attention to disturbances of the second and third portions of the duodenum which were roentgenologically evident in the fluoroscopic examination of patients. I described the fullness and distention that follow the ingestion of food in patients with gallbladder disease as resulting from a reflex atony of the stomach associated with a temporary delay in the emptying of the duodenum, and pointed out that this overdistention of the stomach only exaggerated the delay, and when the stomach was relieved of its intragastric tension it also released the pressure on the retroperitoneal portion of the duodenum. I also mentioned that belching and eructation of gas frequently afforded the patient with gallbladder disease much relief unless he swallowed more air than he really expelled. These changes in the duodenum are not without their experimental data. You have known from your studies in physiology that animals will die within a relatively short time if the duodenum is obstructed or even if segments of isolated loops of the intestine remain closed; further, aspiration of the contents of these isolated loops, when injected into other animals, brings about death within a relatively short time. It has also been experimentally shown that

the giving of large amounts of hydrochloric acid to animals with a partially obstructed duodenum may temporarily relieve the pathologic picture that ensues.

Normally, the reaction of the blood expressed by a pH of 7.4 is slightly more alkaline than water. The pH may be raised 0.02 or 0.03 above this level by such a simple physiologic means as blowing off carbonic acid in voluntary overbreathing, and it can be lowered as much by the lactic acid produced in the muscles in a short, hard sprint. But if the change goes much farther in the alkaline direction, a tetany of alkalosis sets in. Nor can much greater change in the acid direction be tolerated without the symptoms of acid poisoning. The acid-base changes of the body are of two types: those caused by the excess or deficit of carbon or carbonic acid, and those caused by the excess or deficit of supply of buffer alkali available for neutralizing nonvolatile acids, such as lactic, hydroxybutyric, and hydrochloric. The first type is called carbonic acid excess and deficit, and the second alkali excess and deficit, because in it the alkali reserve of the body is increased or diminished.

The acid-base changes resulting primarily from overventilation or underventilation were first noted in physiologic experiments and were found to occur frequently clinically. Grant and Goldman, in 1920, showed by voluntary overventilation that they could produce an alkalosis of carbonic acid deficit with a subsequent development of tetany simulating that produced by the loss of hydrochloric acid. Other observers have noted this condition in encephalitis, and that it occurs not uncommonly in hysteria and occasionally in febrile conditions. The tetany which accompanies the alkalosis either of alkali excess or carbon dioxide deficit appears to be associated with a pH increase in the blood, which occurs in both conditions. This may simulate the tetany produced by the lack of blood calcium. However, tetany may occur when the pH is 7.6 or 7.7 with a normal calcium content. On the other hand, acidosis of a carbonic acid excess can be produced by rebreathing carbon dioxide so that the concentration of free carbonic acid in the blood is increased. This, in turn, is associated with a marked depression of the blood pH and a greater hyperpnea. This has been found by some observers in cases

of emphysema and bronchitis, in which the gas exchange in the lung is markedly hindered. These patients show dyspnea on the slightest exertion.

The physiologic available alkali reserve of the body is in the form of buffer salts. They may go into solution with relatively little pH change, able to neutralize a greater part of acidity or alkalinity as the result of the intake of strong acids or alkalis. This buffer act is illustrated by the behavior of bicarbonate to which hydrochloric acid is added, forming carbonic acid and sodium chloride, thus replacing a strong acid with a weak acid and the hydrogen ion concentration of the mixture of sodium bicarbonate and carbonic acid and sodium chloride is only a small part that would exist if the hydrochloric acid remained free. If, on the other hand, alkali is added to a solution containing sodium bicarbonate and carbonic acid, the alkali reactions with the carbonic acid component, giving sodium bicarbonate and water. Thus, the strong alkaline, sodium hydroxide, is replaced by the weak, the alkaline sodium bicarbonate. Thus a solution containing a buffer mixture of sodium bicarbonate and carbonic acid can receive either a strong acid or strong alkali with relatively small change in the pH .

In the blood the chief part of the buffer is in the form of bicarbonate. About 0.01 equivalent of more alkali is available in the form of alkali hemoglobinate. These two buffers contain buffer alkali enough to absorb nearly 150 cc. of normal hydrochloric acid before the reaction becomes fatally acid. But the chief alkali store in the body is in the buffers of the tissues, which can neutralize about five times as much acid as the buffers of the circulating blood.

The carbon dioxide tension is used to express the concentration of carbon dioxide in the air with which the blood is saturated. When the blood plasma is saturated at body temperature with pure carbon dioxide the plasma dissolves 51 per cent of carbon dioxide as free carbonic acid. If one breathes more deeply and rapidly, the usual carbon dioxide of alveolar air becomes more diluted; in other words, its tension falls and the carbonic acid of the blood falls proportionately.

Thus, in cases of carbonic acid excess which are usually of respiratory origin, conditions exist which prevent a normally

efficient aeration of the blood in the lungs. Clinically it has been found in emphysema, the condition of bronchitis and asthma in which pulmonary gas interchange is interfered with. In asthma and bronchitis it is probably associated with a spasm of the bronchi and bronchioles, while in emphysema it is probably associated with changes in the alveoli. In morphine poisoning carbonic acid excess is frequently seen. Subjectively patients complain of exertional dyspnea; even while at rest these patients do not ventilate their lungs well enough to prevent some carbonic acid increase in the blood. While this carbonic acid excess is not an important clinical consideration, it is enough to explain the respiratory difficulty in patients who have respiratory disease. In carbonic acid deficit, a condition which results when the ventilation is so stimulated that carbon dioxide tension in alveolar air and the blood is reduced below the level necessary to maintain the usual pH in arterial blood, sodium bicarbonate and the carbonic acid ratio increases and therefore the pH rises. This condition is one of respiratory alkalosis.

The effect of the carbonic acid deficit is that the alkali reserve of the blood gradually begins to fall. The diminution of the alkali reserve is regularly noted in persons who go to high altitudes, and may be directly proportional to the fall in barometric pressure. This carbonic acid deficit may result in tetany, and whereas morphine may cause a carbonic acid excess in instances of carbonic acid deficit, morphine is used to combat the condition. Further, there are conditions of changes in the acid-base equilibrium which are associated with alkali excess and alkali deficit. In instances of alkali excess, which are usually associated with the administration of alkali buffer salts or alkali organic salts or in which the body may lose acid by vomiting, we find, as stated before, that the blood bicarbonate and pH increase and if the condition goes far enough tetany may supervene. Also, if there is a retention of alkali salts there may be an increased secretion of sodium bicarbonate in the urine, whereas when gastric juice is lost the bicarbonate salts are held back by the kidneys in an apparent effort to regulate the salt content of the body fluids. In other words, when an individual has an intake of alkali causing an alkali excess, the kidneys try to regulate the excess by excreting more

bicarbonate, whereas in instances of vomiting the regulatory mechanism of the kidneys is such as to prevent the loss of the alkalis.

As a rule, the withdrawal of alkalis in cases of increased alkali excess resulting from overalkalization is enough to prevent any serious damage. The kidneys will continue to excrete the bicarbonate and retain the acid radicals and rapidly restore the blood to normal condition. When the alkali excess is caused by a loss of hydrochloric acid, as occurs in toxic vomiting and pyloric obstruction, simple administration of salt and water may be enough to combat it, and when the total salt content of the body returns to a nearly normal state the kidneys again begin to assume their normal rôle and secrete the excess bicarbonate and restore the blood to its normal acid-base condition. However, the alkali deficit, which is more important clinically, is a condition usually encountered in acidosis of diabetes, diarrhea and nephritis. The alkali deficit may be caused by a loss of blood bicarbonates and secondly by nonvolatile acids such as lactic, hydroxybutyric and hydrochloric acid, which may be retained in the body and therefore exhaust the buffer alkali. In severe diarrhea large amounts of alkali bicarbonate can leave the body by way of the intestine. One of the chief salts of bile and pancreatic juice is alkali bicarbonate and therefore its rapid depletion by means of a diarrhea will cause an alkali deficit. This condition is also seen frequently in patients who have ileostomies, in whom there is a rapid peristalsis of the small bowel. The kidneys excrete only noticeable amounts of bicarbonate when there is a state of alkalosis caused by alkali excess or carbonic acid deficit. However, when the acidosis of alkali deficit occurs, the urine becomes more acid, alkali excretion stops and the excretion of acid is replaced in the form of ammonium salts and titratable acid.

The effects of alkali deficit are evidenced by a lowering of the bicarbonate content and pH at once in the blood. The circulation is increased, tachycardia is noted and hyperpnea may exist simulating the air hunger of Küssmaul. When the cause of alkali deficit is alkali loss, as in diarrhea stools, the urine becomes scanty and occasionally the urinary volume becomes so small that there is a retention of nitrogen and symp-

toms of uremia may supervene. Dehydration of the body rapidly takes place, and it would therefore seem logical that salt and water should again replace the fluid loss as well as alkalis to restore the alkali reserve.

The general therapy of alkali deficit is to give alkalis. However, the fact should not be overlooked that fluid administration is important, and when the gastro-intestinal tract is able to absorb it, it should be given by mouth. However, the intravenous route may be indicated early, and later oral administration may be beneficial. The alkalis may be given in the form of bicarbonate, citrate or acetate of sodium. Intravenously, isotonic sodium bicarbonate may be injected. The amount of bicarbonate to be injected depends on the carbon dioxide content of the blood plasma. The volume of isotonic bicarbonate solution may be made up by $\frac{9}{10}$ per cent sodium chloride, the total volume being sufficient to replace the loss of body fluids. In the acidosis of severe nephritis alkali therapy may temporarily restore a patient to consciousness but its continued use will fail to eliminate retained and continually forming acid products. It may be necessary if dehydration and depletion of body sodium chloride are such that saline infusions may be indicated, but in other types of nephritic and cardiac edema saline infusions are contraindicated. It may be parenthetically added that, in the treatment of diabetic acidosis, glucose, insulin and saline solution form the ideal treatment; bicarbonate does not play the dominant rôle that it formerly did.

In the diagnosis of changes of the acid-base abnormalities the type and severity should be determined. Frequently it is one of alkali deficit or excess, and if it is impossible for the physician to make a blood analysis he can add to a given quantity of urine a small amount of sodium bicarbonate and, if the litmus paper turns alkaline, he can exclude the possibility of an alkali deficit or acidosis. If the urine remains acid, the acid-base balance may nevertheless be normal. Thus it can be said that if the urine turns alkaline no acidosis exists. However, the urine tests should not be relied on but an effort should be made to obtain more accurate blood chemistry determinations to establish the *status quo* of the patient.

In reviewing the evidence presented, it would be reason-

able to emphasize that in cases of alkalosis associated with alkali excess, which are frequently seen in overalkalization, the withdrawal of alkalis may be sufficient to combat the condition. However, when the condition has become so severe that there has been definite evidence of kidney damage, more radical measures may be necessary. Even though the patient may have a peptic ulcer, hydrochloric acid by mouth may be indicated. Large amounts of sodium chloride should be given intravenously and, if vomiting is a persistent symptom, glucose should be given along with saline solution intravenously, to protect the glycogen reserve of the liver, which may be depleted in this period of starvation. Ammonium chloride and other acidifying salts may be used when indicated. The important clinical consideration in alkali excess is to recognize that alkalis should be given to patients who may tolerate them, and here again prevention is the best cure of the disease.

In cases of carbonic acid excesses, the treatment of the underlying respiratory difficulty or atmospheric condition is the logical method of approach; the same holds true for carbonic acid deficit. When an alkali deficit exists, uncomplicated by diabetic acidosis, and particularly noteworthy in cases of diarrheal conditions, it is simple enough to restore the alkali; however, here again it is to be borne in mind that, with the rapid peristalsis of the intestinal tract and the little time required for absorption, rapid emaciation may ensue, a depletion of the liver glycogen content goes hand in hand, and in restoring the fluid balance glucose should again be administered intravenously to protect hepatic function. Finally, let me emphasize that when vomiting is present there is not only a loss of hydrochloric acid but also an inanition of the body. All these conditions call forth a keen, analytic experience in bedside medicine, a comprehension of disturbed body metabolism and a scientific approach to the problem, in order to serve the best interests of the patient.

CLINIC OF DR. ROLAND P. MACKAY

ST. LUKE'S HOSPITAL

THE TREATMENT OF GENERAL PARESIS

PRACTICALLY all syphilis of the nervous system could be prevented by adequate treatment in the primary and secondary stages of the disease. The great prevalence of neurosyphilis is, therefore, eloquent testimony to the mismanagement of cases in these early stages. After the nervous system has been attacked, success is much more difficult to achieve, and the rules of the game are much more strict. The great majority of American physicians today are untrained in the proper treatment of neurosyphilis, and frequently leave the job less than half done. Their efforts are, furthermore, hindered by the financial limitations of their patients, and by their lack of cooperation. If the problem of neurosyphilis is ever to be solved, the average physician must become more thoroughly familiar with the correct methods.

Neurosyphilis is much more responsive to treatment than any other chronic disease of the central nervous system. So true is this, that when a patient is found to be suffering from neurosyphilis rather than multiple sclerosis, chronic encephalitis, or one of the degenerations, he is entitled to congratulation. Various types of syphilis of the nervous system differ widely in their "curability," tabes dorsalis being least favorable and general paresis much more amenable. It has been only during the past twenty-five years, however, that general paresis could be treated with any measurable success, and this improvement in prognosis has been entirely due to the employment of fever and certain pentavalent arsenical compounds, such as tryparsamide. With these methods, properly employed, from one third to one half the patients with general

paresis can be restored to useful life, while a goodly additional number can be benefited materially.

In those cases of general paresis characterized by euphoria and excitement rather than by depression or simple dementia, and in which objective neurologic signs are absent or few, the prognosis is especially good. In general, the likelihood of success in the treatment of general paresis is inversely proportional to the number and severity of such objective neurologic signs as the Argyll Robertson pupil, ocular or other palsies, optic atrophy or tabetic manifestations. On the other hand, success depends primarily upon the thoroughness and care with which certain principles of management are followed. Without adherence to these principles, even the most favorable cases will terminate in failure. The 2 cases presented here illustrate some of the points which should be emphasized regarding the treatment of general paresis. In the 2 cases the patients first came under observation seven years ago, so that the success of their treatment has now been reasonably well established. Nevertheless, certain improvements in their management will have to be indicated—improvements which represent experience acquired during the intervening period.

ACQUIRED GENERAL PARESIS

Case I.—On July 2, 1930, an unmarried white man, forty-five years of age, was admitted to the neurologic service at St. Luke's Hospital, Chicago. For nine years he had been under vigorous treatment for neurosyphilis elsewhere in the city. On August 26, 1921, his spinal fluid contained 62 cells per cubic millimeter, and gave a 4 + Wassermann reaction, positive responses to tests for globulin, and a colloidal gold curve of 5542100000. During the succeeding years his serologic formula had been temporarily improved with regard to the gold curve and cell count, but his Wassermann reaction had remained constantly 4 +. He had received numerous courses of neoarsphenamine, silver arsphenamine, tryparsamide and mercury. In September, 1926, his spinal fluid Wassermann reaction was still 4 +, the cell count 6, globulin tests positive, and the gold curve 5544321000. Nearly two years later, in April, 1928, his spinal fluid still gave a 4 + Wassermann reaction, a cell count of 6, and a positive Ross-Jones test but the colloidal gold curve had been reduced to 1233321000.

Upon admission the patient was so irrational and disturbed that no history could be obtained of the recent course of his illness. He was confused and disoriented, and unable to cooperate with his examiner. He was so excited that restraints had to be used to prevent his getting out of bed and walking around the ward unclothed. His speech was slurred and at times incoherent.

The general physical examination was negative, but his pupils were small, irregular and reacted better in accommodation than to light. There was no motor weakness. The tendon reflexes were present and equal in the upper extremities, but entirely absent in the lower. There were no definite disturbances of sensation and no pathologic reflexes. The diagnosis, taking into consideration the known history and serologic data, was acquired taboparesis.

Treatment was begun at once with deep injections of 2 per cent sulfur in olive oil into the muscles of the lateral aspects of alternate thighs. Beginning with 1 cc., the dose was gradually increased. Injections were made about twice a week, and always in the evening, since the elevation of body

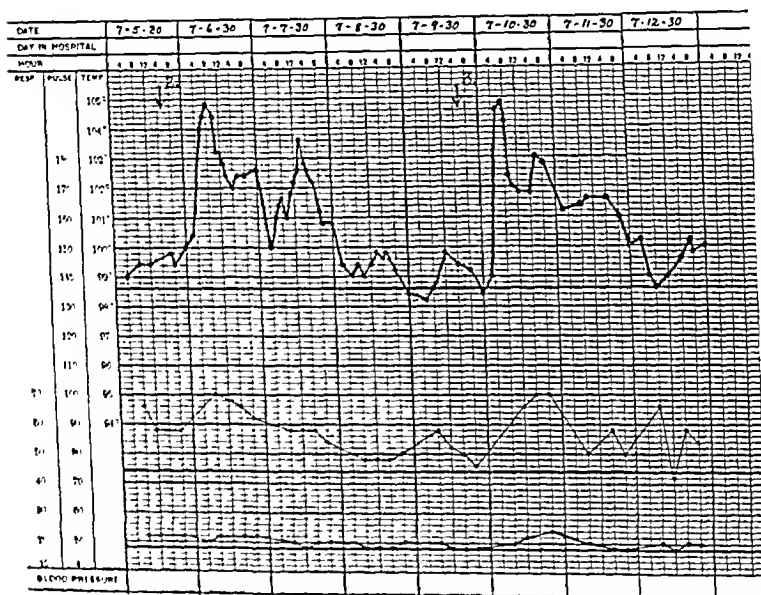


Fig 39 - Curves of the temperature, pulse and respiration following the second and third intramuscular injections of 2 per cent sulfur in oil (Case I). The doses used in these two injections were 2 and 3.5 cc. respectively.

temperature occurred about twelve hours later. Figure 39 presents temperature, pulse and respiration curves following the second and third injections, and Table 1 gives details as to the dates of injection, the doses used and the height of fever attained following the 11 injections in the course. Study of all the temperature curves during the course revealed that the patient's temperature was above 104° F. for a total of nineteen hours; above 103° F. for an additional twenty-two hours, and above 102° F. for one hundred and twenty-four hours more, a total of one hundred and sixty-five hours above 102° F.

After the conclusion of the course of 11 sulfur injections no further fever was given until nearly four weeks later, when intravenous injections of

largely of sluggishness of his pupillary reactions to light and absence of knee and ankle reflexes, did not undergo any change.

After his dismissal from the hospital, he was treated in the St. Luke's outpatient clinic. Table 3 gives detailed information regarding the treatment for the next six years and more. He received, it will be noted, almost constant treatment with mercury, bismuth in different forms, and tryparsamide from the time of his dismissal from the hospital, November 11, 1930, to March 31, 1933—or for two years and four months. During that time frequent examinations of his blood and spinal fluid were made, and it was found that the serologic reactions were steadily becoming more normal. On April 10, 1933, his mental state

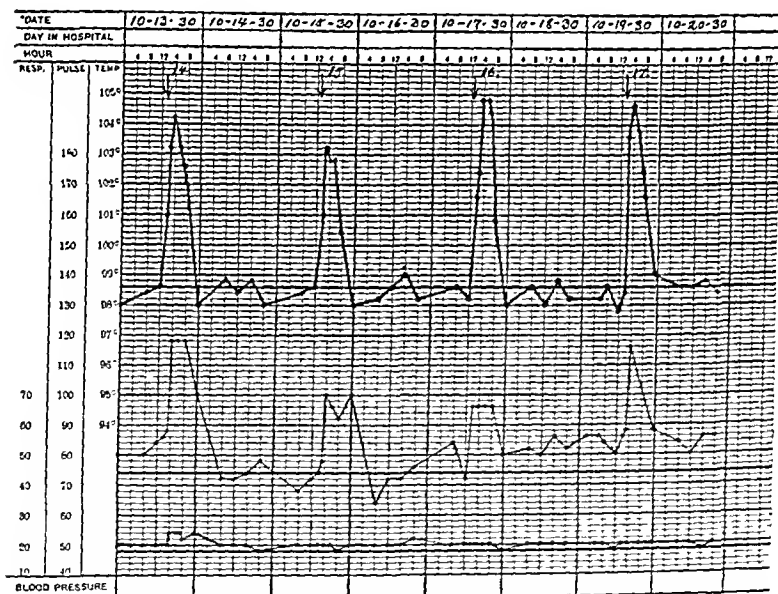


Fig. 40.—Curves of the temperature, pulse and respiration following the last 4 intravenous injections of typhoid-paratyphoid vaccine (Case I). See Table 2 for the doses administered.

was excellent, and his cerebrospinal fluid practically normal. Thereafter his clinical and serologic condition remained unchanged without further treatment until December, 1935, or for a period of two and one-half years. At this time he began to have a few lightning pains, and a course of 15 intramuscular injections of bismarsen was given. About a year later, in January, 1937, his blood Wassermann showed some tendency to become mildly positive, and another course of 15 bismarsen injections was given. In June, 1937, his clinical examination showed normal mentality, absent patellar and Achilles reflexes, absent

TABLE 3
CHEMOTHERAPY USED IN CASE 1 (ACQUIRED TABOPARESIS)

Date	Preparation	Amount	Interval	Number	Remarks
1/2/31 to 1/10/31	For salicylate in oil	2 cc	Weekly	15	Spinal fluid: Clear, colorless, cells 5, Ross-Jones and Pandey faintly positive; Wassermann reaction negative; gold curve 2555542400.
1/10/31		Course stopped due to "reaction," nature not stated.
1/17/31 to 1/11/31	Trypanamide	1 Gm 1.5 Gm 2 Gm	Weekly	3	
5/17/31 to 7/12/31	Bismarck	0.2 Gm	Weekly	17	Followed by rest period.
9/17/31		Blood Wassermann reaction 25 per cent positive; Kahn + +.
9/18/31 to 11/23/31	Bismarck	0.2 Gm	Semiweekly	20	Followed by rest period of two months.
1/14/32		Blood Wassermann reaction 25 per cent positive; Kahn + +.
1/26/32 to 5/13/32	Bismarck salicylate in oil	2 cc	Weekly	15	Followed by rest period of 2 months.
6/23/32		Blood Wassermann reaction 10 per cent positive; Kahn +.
6/24/32 to 8/30/32	Bismarck salicylate in oil	2 cc	Semiweekly	20	Followed by rest period of 2 months.
10/13/32		Blood Wassermann reaction 10 per cent positive; Kahn +.
12/16/32 to 3/31/33	Trypanamide intravenously	2 Gm	Weekly	15	Spinal fluid: Clear, colorless, cells 3, Ross-Jones and Pandey very faintly positive; Wassermann reaction negative; gold curve 00122210000.
4/10/33		Spinal fluid: Clear, colorless, 3 cells, Ross-Jones and Pandey very faintly positive; Wassermann reaction negative; Kahn negative; gold curve 00122221000.
11/17/33		Examination: Mentally normal. Neurological: As at first. Blood Wassermann reaction negative; Kahn +.
12/11/31		Blood Wassermann reaction negative; Kahn negative. Spinal fluid completely negative except gold curve 1222110000.
January, 1935		"Has had a few lightning pains."
12/13/35 to 3/13/36	Bismuth arsenphenamine sulfonate	0.2 Gm	Weekly	15	Spinal fluid bloody; Wassermann reaction negative; Kahn negative.
4/18/36		Blood Wassermann reaction 50 per cent positive; Kahn +.
1/18/37		
2/23/37 to 5/11/37	Bismuth arsenphenamine sulfonate	0.2 Gm	Weekly	15	Blood Wassermann reaction negative. Kahn +. Spinal fluid completely negative. Total

6/26/37 Examination: Mentally normal. Neurological: As at first. Blood Wassermann reaction negative. Kahn +. Spinal fluid completely negative. Total protein 25 mg. per 100 cc. Gold curve 0011100000.

six years. His objective neurologic (clinical) picture had continued unaltered for the same length of time, and his serologic negativity had continued since early in 1933, a period of over four years, without essential change.

JUVENILE PARESIS

Case II.—In October, 1930, a young white man, twenty-two years of age, was referred for treatment of juvenile paresis. Since the age of fifteen he had been treated for congenital syphilis by a syphilologist who had used nothing except orally administered mercury and potassium iodide. In October, 1930, he began to exhibit euphoria, pressure of activity and emotional outbursts. At times he was disoriented and destructive and became very antagonistic to his mother. His behavior was so disturbed at that time that he was sent directly to the Cook County Psychopathic Hospital. In that institution he was in a manic state, talking incessantly about his having received syphilis from his "unfaithful father," making efforts to "help the other patients spiritually," and in general exhibiting destructiveness and a disturbed sensorium. The blood Wassermann and Kahn reactions there were positive, and the cerebrospinal fluid revealed a 4 + Wassermann reaction and a colloidal gold reaction of 5555554321. He was declared insane and committed to the custody of his mother. He was then placed in a private sanitarium for treatment.

Neurologic examination revealed him to be abusive, destructive and unmanageable. He tore the bedclothes into strips, was talkative, resisted the efforts of his attendants, refused all medication and had to be restrained. The right pupil was larger than the left and both were irregular and did not react to light. The reaction in accommodation was very feeble. Articulation was normal. Both upper central incisors were peg shaped and notched. There was a marked scoliosis of the dorsal spine. There was no motor paralysis or definite disturbance of tone. The tendon reflexes were normal in the upper extremities but absent in the lower. Abdominal reflexes were present only in the upper half, but the plantar reflexes were normally flexor. There was a slightly positive Romberg reaction and moderate ataxia in the lower extremities. Sensibility to touch, pain and temperature was normal, as was position sense, but vibration sensibility was practically absent at the ankles. The diagnosis was juvenile taboparesis.

Treatment was instituted at once with 2 per cent sulfur in olive oil, injected in regularly ascending doses into the muscles of the lateral aspect of alternate thighs. The first of these injections consisted of 1 cc and the tenth and last of 12 cc. Thus each injection exceeded the preceding by an average of a little more than 1 cc. Each injection was given in the early evening and the elevation of temperature began some twelve hours later and lasted on the average for nearly two days. The highest temperatures attained following each of the injections were as follows (F.): 102.6, 103, 103.8, 103.2, 102.2, 102.2, 103.6, 104, 103.2, 103.6.

Following this series of injections of sulfur, the patient was allowed two days of rest after which intravenous injections of typhoid-paratyphoid vaccine were begun. These injections were each given in the morning and were followed within an hour by a chill and elevation of temperature lasting on the

average for six or more hours. Injections were given on alternate days, the doses and heights of temperature attained being as follows:

30 million	101.6° F.
175 million	103.2° F.
350 million	102.8° F.
570 million	101.6° F.
1000 million	102.8° F.
2000 million	103.4° F.
3500 million	102.6° F.

In the combined courses of sulfur and typhoid vaccine injections the patient's temperature exceeded 104° F. once, 103° F. eight times, 102° F. six times and 101° F. twice.

On November 13, 1930, following the fifth sulfur injection, 3 Gm. of tryparsamide were given intravenously and continued each week for ten weeks, with careful ophthalmologic control. Thus fever and tryparsamide were given concurrently. During this whole time he steadily improved in his mental reactions. He became quieter, more rational and cooperative, and emotionally better adjusted until he was dismissed from the hospital on January 7, 1931, exactly ten weeks after his admission.

The chemotherapeutic management of this patient is summarized in Table 4. In general, he received consistent and almost constant treatment with tryparsamide, bismuth, mercury and potassium iodide for nearly two years. The various courses were usually followed by a month or so of rest before another was begun. The cerebrospinal fluid Wassermann first became negative in August, 1931, nearly a year after treatment was begun, but the colloidal gold reaction showed a gradually decreasing abnormality for more than two years longer and was first completely negative in April, 1935. During this whole period his mental state remained quite normal, but the large, unequal Argyll Robertson pupils and the absent tendon reflexes and vibration sense in the ankles remained unchanged. Subsequent examinations of blood and cerebrospinal fluid have remained quite negative, and at the present time (July, 1937) he is normal mentally and is regularly employed as a hospital orderly and does good work.

Comment.—The first important deduction to be made from these 2 successfully treated cases is that the use of fever accomplished in each what previous chemotherapy had failed to do. In the second case (juvenile taboparesis) this previous treatment had been very poor but in the first (adult taboparesis) it had been vigorous and sustained. In both, chemotherapy had proved inadequate. The results obtained by fever therapy were almost immediately evident in the prompt improvement of the patients' mental condition. The patient

TABLE 4
DETAILS OF THE CHEMOTHERAPY USED IN CASE II (JUVENILE TABOPARESIS)

Dates.	Preparation.	Amount.	Interval.	Number.	Remarks.
11/13/30 to 1/27/31	Trypsamide.	3 Gm.	Weekly.	10	
1/30/31 to 2/18/31	Ung. hydrarg.	1 drachm	Daily.	15	Inunctions.
2/23/31	Blood Wassermann negative. Blood Kahn 75 per cent positive. Spinal fluid clear, colorless; 1 cell, Pandy faintly positive. Wassermann 100 per cent positive; gold curve 1234321000.
2/26/31 to 1/17/31	Bismuth sodium tartrate 1.5 per cent.	2 cc.	Semiweekly.	15	Normal mentally at conclusion of course.
5/13/31 to 6/10/31	Unguentum hydrargyri.	1 drachm	Daily.	24	Inunctions.
8/11/31	Spinal fluid completely negative except gold curve 1223421100.
8/21/31 to 10/26/31	Trypsamide.	3 Gm.	Weekly.	10	
11/17/31 to 2/1/32	Saturated solution KI.	x gr.	B. I. D.		
3/5/32	Spinal fluid completely negative except gold curve 0122211000.
3/5/32 to 3/26/32	Unguentum hydrargyri.	1 drachm	Daily.	18	Inunctions.
7/25/32 to 8/6/32	Unguentum hydrargyri.	½ drachm	Daily.	12	Severe lightning pains. Neurological examination: Signs unchanged; mentally normal.
9/9/32	Spinal fluid clear, colorless; Wassermann reaction 50 per cent positive; gold curve 0023310000.
9/9/32 to Sept., 1933	Potassium iodide; Unguentum hydrargyri.	gr. x 1 drachm	Three or four courses.	Medication given at varying intervals.
Sept., 1933	Spinal fluid clear, colorless, cells 0; Wassermann negative; Pandy and Ross-Jones negative; gold curve 122221000.
April, 1935	Spinal fluid completely negative, including gold curve 0000000000.
May, 1936	Spinal fluid completely negative, including gold curve 0000000000.

with adult taboparesis showed mental improvement of unmistakable degree six weeks after the start of sulfur injections, while the patient with juvenile taboparesis began to show improvement almost at once after the fever treatment was instituted. The serologic improvement was much slower in appearing, however. The spinal fluid findings in the case of adult taboparesis were essentially unchanged eight months after fever therapy was started, even though vigorous treatment with tryparsamide and bismuth accompanied and followed the fever. In this patient the blood Wassermann reaction became essentially negative within a few months but the spinal fluid findings first showed significant improvement nearly two years after fever therapy was given. In the patient with juvenile taboparesis, however, the colloidal gold curve showed definite improvement three months after treatment was started, and the cerebrospinal fluid Wassermann became negative in less than a year following the fever therapy. In this case, likewise, vigorous follow-up treatment with tryparsamide, mercury and bismuth was carried out.

That the mental and serologic improvement in these patients is to be attributed more to the fever than to the chemotherapy is shown by the fact that earlier treatment with the same chemotherapeutic substances had not only failed to accomplish the improvement, but had actually permitted the development of active general paresis. The credit for the good results in both these cases is rather to be attributed to the *combined* effects of the fever and chemotherapy than to either factor alone. It is a mistake to rely solely on fever, no matter by what method induced, for success in the treatment of general paresis. In all cases it is wise to accompany or follow the fever with tryparsamide, bismuth and mercury. If malaria is used as the method of producing fever, the tryparsamide must be withheld until the course of fever is ended, since the tryparsamide will terminate malaria. The chemotherapy—with tryparsamide, bismuth, bismuth arsphenamine sulfonate, mercury and iodide—must be vigorously pushed until the serologic reactions are all negative, allowing only such rest periods as may be necessary to prevent any toxic effects from the metals. Alternation from one preparation to another and back again also assists in avoiding metal poisoning. If this continued

treatment fails to reduce the serologic findings to normal, a return to fever therapy must be tried.

It is important to note that in both our cases of taboparesis the paretic elements of the syndrome, both mental and serologic, responded completely to the treatment given, but the tabetic elements remained unchanged. This is the invariable result. We have never seen lost knee and ankle reflexes brought back, nor Argyll Robertson pupils restored to their normal state, no matter how much treatment may be given. Fever therapy, however, is considered effective in many cases in halting the progress of the disease and preventing the advance of optic atrophy, ataxia, and other tabetic changes.

Methods of Producing Fever.—It is important to point out certain conclusions that may be drawn regarding the methods used to produce fever in these 2 cases. We have used typhoid vaccines in the treatment of general paresis for over ten years. Intramuscular injections of sulfur in oil were used for some years but have gradually been abandoned chiefly because of the pain and discomfort they entail. The typhoid vaccines have been found highly satisfactory because of the fact that they do not subject the patient to another disease, such as malaria, because they are effective in producing adequate fever in our hands in the great majority of patients, and because they are capable of very accurate measurement and the production of exactly the desired amount of temperature elevation with extreme nicety. Typhoid vaccines, furthermore, have in our hands produced excellent clinical and serologic results without a single fatality. They are highly convenient, require a minimum of nursing care, and give no difficulty in terminating the fever, as sometimes occurs with malaria.

In the cases reported here we were much more conservative regarding dosage of the vaccine than we have since become. As a result, the fever reactions obtained in these cases were not so high or consistent as we have since learned to produce. Good results were nevertheless obtained, and we believe others can obtain equally good results with a little experience in handling the vaccines. We are persuaded that failures in other hands have been due to lack of skill in using the method, with the result that insufficient amounts of fever were obtained.

It is not yet known why fever produces remissions in

general paresis. In general, fever invoked by infection is a reaction to a foreign protein, and is accompanied by leukocytosis (except in malaria), antibody formation, and other important biologic processes. These additional phenomena have great value in overcoming the infections which produce them, and no one supposes that the elevation of body temperature is the sole beneficial factor in the usual febrile reaction to infection. It is thus not unreasonable to think that these additional reactions may play a rôle in overcoming neurosyphilitic infections when malaria or typhoid vaccine is used.

Nevertheless, on the theory that simple elevation of the body temperature is sufficient in the treatment of neurosyphilis, certain "physical" methods have recently been employed to raise the temperature. In rapid sequence diathermy, inductothermy, and finally the "hypertherm" were utilized. More or less favorable results were reported in the treatment of general paresis, but the striking success of these "physical" methods in the treatment of gonorrhea lent an additional glamour to the procedure. All the "physical" methods depend upon the simple application of more heat to the body than can be dissipated. They all require highly complicated equipment and much technical skill, and hence involve considerable expense. They are, therefore, beyond the financial reach of many patients and are often not available at any price in many parts of the country. Such "physical" methods are, furthermore, dangerous, even in expert hands.

Again, it appears to be more in accordance with the rôle played by fever in ordinary infections to use "biologic" methods, such as malaria or typhoid vaccines, in the treatment of general paresis. The good results obtained in the cases reported here, and in many other cases that might be cited, seem to indicate that the extremely high and prolonged temperatures necessary to obtain good results by the "physical" methods in general paresis are not necessary with malaria or typhoid vaccines. It is as if the parallel immunologic reactions which accompany fever produced by these "biologic" methods make excessively high and prolonged temperatures unnecessary.

The cases reported here were successfully managed, finally, because the patients were persistently and thoroughly treated. They cooperated in the minutest detail and did not abandon

treatment as soon as definite improvement was achieved. The tendency of so many patients to discontinue treatment because of discouragement, financial inability to carry on, or even the physician's indifference, is the greatest single factor in the failure so often encountered in the treatment of general paresis. Neurosyphilis is like diabetes mellitus in that the results of treatment depend first of all upon the intelligence and cooperation of the patient or his responsible relatives in following instructions. Given the combination of persistence on the part of the physician and interested cooperation by the patient or those responsible for him, and modern science can accomplish a great deal more in the treatment of general paresis than is generally supposed.

CLINIC OF DRS. EDWIN W. PASSARELLI AND
LEROY H. SLOAN

COOK COUNTY HOSPITAL

UNDULANT FEVER

History and Bacteriology.—Undulant fever is primarily a disease of animals which may be transmitted to man. The animals directly concerned are goats, cattle and swine. The disease is not new, having been discovered in humans originally on the island of Malta. Marston gave the first account of the clinical picture and postmortem findings under the name of its most striking symptom, Mediterranean remittent fever. Bruce (1887) discovered the causative organism in goats, naming it *Micrococcus melitensis*. The etiologic agent of infectious abortion in cattle was described by Bang (1897) who named it *Bacillus abortus*. Evans (1917) compared these two organisms and showed that they could not be differentiated morphologically, bacteriologically, or chemically. The isolation of *B. suis* from swine, similar to the above two, was first reported by Traum (1914).

Epidemiology.—The spread of undulant fever has been demonstrated to occur in one of two ways, either through direct contact with infected animals and meats, or through the ingestion of contaminated dairy products. That butter, cheese and ice cream are a factor has been proved by the demonstration of viable organisms in them in spite of their salt content and the lowered temperature at which they are kept. All our cases could be traced directly to ingestion of unpasteurized milk, to contact with infected cattle, swine, or goats, or infected carcasses. Two of our cases, a mother and son, came into direct contact with a goat. The mother contracted her infection through drinking the unpasteurized goat's milk and the son through playing with the animal. There were 14

males and 7 females in the group with the greatest number of cases occurring in the age group between twenty and forty years. This is in proportion to the findings in larger series. The duration was from three to eighty-eight weeks with the average at twenty-eight weeks.

SYMPTOMS and SIGNS

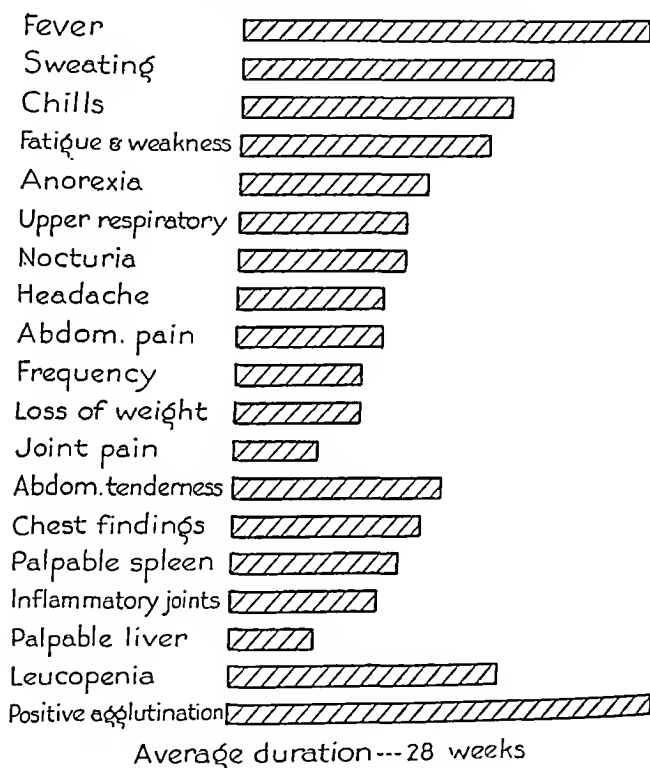


Fig. 41.—Relative frequency of symptoms and signs in our cases of undulant fever.

Symptoms.—In the past year on our various services,¹ we were able to observe 21 cases of undulant fever. The incubation period of the infection is from five to twenty-one days with the average reported at fourteen days. The onset of the condition is usually gradual, though in some cases it may be

¹ (1) Cook County Hospital, Chicago. (2) Private practice of Dr. LeRoy H. Sloan. (3) Private practice of Dr. Clyde R. Landis

sudden and there are no definite prodromal symptoms to signify it. In most of our cases the initial complaints are of some upper respiratory condition with the attendant symptoms of cough, sore throat, dysphagia, pain in the neck, or pain on respiration, fever, feeling of chilliness or actual chill, and fatigue. The cough may be dry and tickling or it may be moist with scanty expectoration of grayish mucoid material. Blood streaks may be present in the sputum. These appeared gradually in a period ranging from a few days to months. In

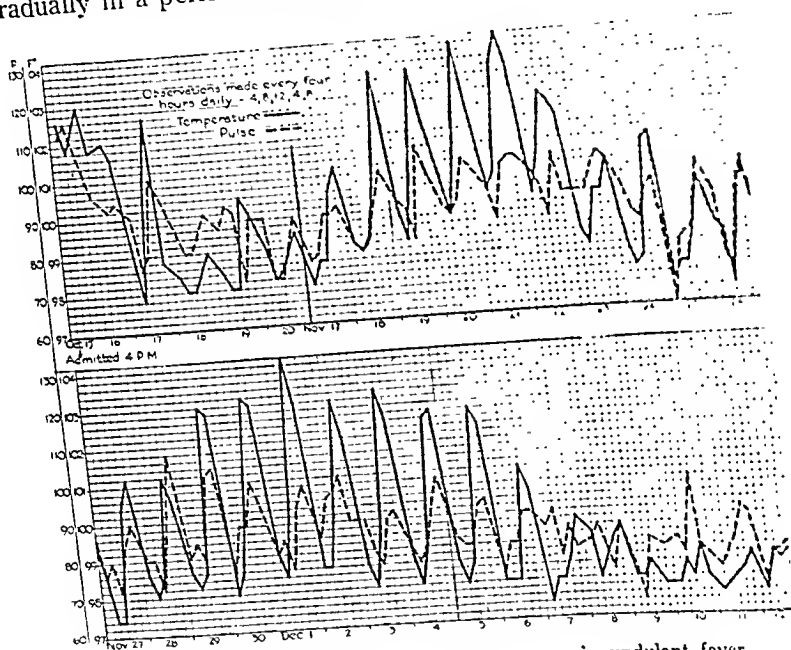


Fig. 42.—Typical temperature and pulse curve in undulant fever.

other cases the onset was sudden, being characterized by frank chill lasting as long as one hour, associated with fever and sweating. In our cases fatigue and weakness were prominent symptoms. Anorexia was marked to the extent that it is partly responsible for the pronounced loss of weight. That the genito-urinary system suffers also, is indicated by nocturia, frequency, and albuminuria. Headache and abdominal pain are common and may be severe. Constipation occurred in 5 and diarrhea in 3 of our cases. General muscle and joint pains

are common and joint involvement resembling that of rheumatic fever is not uncommon. Sweating is a *very* prominent feature; the sweats are drenching in character and seem to have a peculiar sour odor. Epistaxis was noted in 2 cases. The fever is septic in character and of the daily remittent type. It reaches a peak of about 105 and over a period of time shows waves and undulations that are responsible for the name of the infection. As the fever declines, the patient feels better and then a few days later a relapse occurs and the symptoms recur. Irritability and psychomotor phenomena are common. (One of our patients had a psychoneurosis with a depressive state diagnosed before his undulant fever. The psychoneurosis cleared entirely with the control of the undulant fever.) In general, the symptoms are those of a septicemia.

Signs.—There is a paucity of physical findings. The patient when seen is quiet, apathetic and weak. His response is sluggish though he may not look acutely ill. Sweating is profuse and constant. There may be a few râles in the lungs usually found in the bases, slight impairment of resonance, and occasionally bronchial type of breathing in the lower portions or around the hilus. Because of these findings in the lungs, many of our patients were x-rayed to rule in or out a pneumonia, bronchitis, or other lung condition. The x-ray films consistently showed increased hilar markings and in some, actual increase in the density of the hilus glands. Some showed infiltration extending from the hilus areas outward. The abdomen may be rounded and tympanitic. Voluntary rigidity may be present because of underlying tenderness. The *spleen is usually palpable and tender*. Occasionally the liver is palpable, *at times much enlarged*. Usually tenderness is elicited over some portion of the bowel. Swollen, painful, tender, red joints resembling the inflamed joints seen in rheumatic fever are sometimes noted. These are usually the larger joints. There is little tendency for multiple or sequential involvement as is seen in rheumatic fever. The pulse is slow in proportion to the temperature.

Laboratory Findings.—The urine is usually negative but occasionally shows albumin in quantity from a trace to 3 plus.

Blood culture for recovery of the *Brucella* is a positive

diagnostic procedure and occurs most frequently early in the disease.

Blood counts show a moderate secondary anemia with a leukopenia which may be as low as 3000 white blood cells per cubic millimeter. The reduction in white cells is mainly in the polymorphonuclear neutrophils with a relative lymphocytosis. mainly in lymphocytes, the cells responsible being the large mononuclears.

The *specific* diagnostic procedures are, in the order of their importance, blood culture, agglutination test, guinea-pig inoculation and skin test. Blood culture, when positive, is conclusive evidence of infection. The technical difficulties of culture and prolonged incubation do not tend to make this method *practical* as a quick diagnostic procedure. It should be done as a check on the clinical findings and other laboratory tests. Next and *most practical is the agglutination test*. This is performed in the usual manner and a minimum titer of 1:80 is mandatory for specific diagnosis. Normal persons sometimes show agglutination to the *Brucella* in titers below 1:80. Nonspecific cross agglutination is sometimes found with the *Bacterium tularense*. Inoculation of the guinea-pig intraperitoneally with blood or in the groin with washed sputum, fecal extract, urine taken aseptically, or crushed tissue, will show the production of agglutinins in the guinea-pig's blood after about five weeks. The skin test is performed like any other skin reaction, by the injection of 0.05 cc. of a dilute killed suspension of organisms intradermally. The reaction is read in twelve, twenty-four and seventy-two hours; positive reaction being noted by varying degrees of induration. No attention is paid to reactive hyperemia. *Induration* is the cardinal sign in a positive reaction. Minor degrees of redness will lead to confusion in interpretation in this reaction.

In practice the agglutination test and the skin test are the easiest and quickest to perform. Care must be exercised in their interpretation, and results should, where possible, be checked by blood culture or guinea-pig inoculation.

Therapy.—The first thought and action in the therapy of this infection should be directed to *prophylaxis*. Contamination of veterinarians, persons working in slaughter houses, butcher shops, or coming in contact with infected animals or

carcasses can be prevented by the wearing of gloves, care in the prevention of lacerations, and cleanliness before eating. The absolute prohibition of the consumption of raw meat, blood, milk, etc., by workers in the stock yards and dairy depots, is imperative. Veterinarians should use aseptic precautions. It is of primary importance that milk from infected areas should be pasteurized before shipment to prevent spread to distant places. Also milk should be pasteurized before being made into butter, cheese or ice cream. Laboratory workers become infected despite every precaution, thus leading to the conclusion that infection probably takes place via the respiratory tract. Thus they should wear masks. Prophylactic vaccination has not been successful either in the animal or man. The eradication of the infection depends on the elimination of the source; that is, stamping out the disease in goats, cows, and pigs.

The active treatment is symptomatic. It is the same as that of any protracted fever. Bed rest, adequate fluid intake and adequate high caloric diet are essential. Good nursing is necessary. The fever should be controlled by sponging or hydrotherapy. Judicial use of antipyretics is indicated. Chills are cared for by external heat and the intake of fluids. Isolation of the patient in the ward or home should be done, certainly as regards stools, urine, sputum and articles used by the patient. This appears to be proper because of the excretion of the organism in these products although infection through human contact has not been proved. Joint pains and inflamed joints are cared for as in rheumatic fever. The bowels should be kept open. Headache may be relieved by one of the coal-tar analgesics. Stools and urine should be disinfected and open abrasions on the skin of the attendant should be covered.

Specific therapy developed recently in the line of intravenous antiseptics, serums, vaccines, and filtrates has been *indifferently* successful. Intravenous mercurochrome (22 cc. of a 1 per cent solution) and trypaflavine (0.20 Gm. intravenously once repeated) have been used with no results or only slight benefit. Intravenous acriflavine (0.5 to 1 per cent solution) in the hands of Beattie and Rice gave good results. Others noted severe reactions. Neoarsphenamine and neo-

salvarsan have not been successfully used. Methylene blue (0.05 Gm. twice daily by mouth for two or three days in capsule) was only partially beneficial. Colloidal metals have failed to control the disease. Hughes, in 1897, reported the unsuccessful use of the following drugs: quinine, bismuth, arsenic, hydrocyanic acid, carbolic acid, boracic acid, chlorine, salol, aconite, colchicum, eucalyptus, turpentine, salicylic acid, antipyrine, antifebrin, phenacetin and resorcin.

Hardy and his associates recommended therapy by means of a heat-killed *Brucella abortus* vaccine, standardized at 2 billion organisms per cubic centimeter. This vaccine is given by deep subcutaneous injection at three-day intervals, in average dosage of 0.25 cc. for 3 injections followed by 1 cc. injections. The first 1 or 2 of these are usually followed by reactions, but these gradually diminish as the course proceeds. Sometimes the site of injection becomes indurated. O'Neil's vaccine is detoxified by treating the cultures with nitrous acid. The vaccine is standardized at 200 million organisms per cubic centimeter and given by subcutaneous injection in doses graduated from 0.5 to 5 cc. His patients, 5 in number, did not have reactions. Others have not had this experience.

It seems more probable that the value of vaccine lies more in the intensity of the general reaction evoked than in any specific effect. The type of vaccine used, apparently, has little to do with the outcome. The toxic effect of vaccines also must be borne in mind.

Huddleson and Johnson, in 1933, described "Brucellin." It is a sterile bouillon culture filtrate prepared from all the varieties of *Brucella*. The patient is tested intradermally, with from 0.05 to 0.1 cc. for sensitivity to the filtrate. If negative, the recommended dosage is 4 intramuscular injections of 1 to 5 cc. at three-day intervals. Injections are followed by an exacerbation of symptoms followed by a gradual defervescence. Results with toxic filtrate are dependent on "shock." Possible harm from toxin should be carefully considered.

O'Neil in 1933 treated cases with a goat antiserum produced by cultures treated with nitrous acid. Later, Wherry, O'Neil and Foshay (1935) used antiserum produced in goats by a formalin-killed culture subsequently detoxified by nitrous

acid. Dosage usually employed is 20 cc. per day for three days, given either intravenously, intramuscularly or subcutaneously. Results have not been entirely satisfactory. The authors state: ". . . we consider the time of administration an important factor in successful therapy and think it advisable to use it early in the course of illness, preferably before the fourth month of the symptoms." Human serum from recovered cases of undulant fever has been used with some success. Results with antiserum are generally favorable but in most cases are only temporary. These temporary benefits are encouraging and lead to the conclusion that concentrated serum might be more efficacious. This type of therapy may be advocated for the acutely ill patient. Convalescent human serum is much less likely to produce an untoward reaction than are the various animal sera.

Foreign proteins have been used as a therapeutic measure. These range from sterile milk, typhoid vaccine to specially prepared bacterial proteins derived from the *Brucella*. Results depend more upon "shock" phenomena, than upon specific reaction, for amelioration of symptoms.

Artificial fever as a mode of therapy is used. Fever of 39° C. (102.2° F.) for three hours to 41.5° C. (106.7° F.) for five hours produced by high frequency oscillator or carbon filament lamp, has been beneficial. The number of cases so treated is small but favorable results support the contention that a febrile reaction is an important factor in combating the infection.

Blood transfusion may be of benefit, especially in children and those patients who are anemic. (One of our patients began a remission promptly after transfusion.)

In summary we may say that there is no specific therapy for undulant fever. In some cases the various specific vaccines, sera and filtrates seem to work well, but the results are difficult to calibrate against nonspecific therapy. Combinations of different types of therapy do not alter the course of the infection more than any one type alone. However, combination of specific and nonspecific measures should be instituted on diagnosis, and the subsequent response should determine its continuance one way or another. Each case is an individual problem and the treatment will rest on the response of the

individual patient to various measures demanded by the judgment of the physician.

Complications.—Complications that we encountered in undulant fever were arthritis, arthralgia, neuralgia, endocarditis and myocarditis, adenitis, urosepsis, meningismus, phlebitis, hepatitis, persistent jaundice, persistent weakness, and neurasthenia.

Differential Diagnosis.—The clinical diagnosis of the condition is difficult unless epidemiologic information is volunteered, for there is nothing pathognomonic in the history and physical examination. The prime features that cause the patient to seek aid—fever and chill, drenching sweats or cough with expectoration of blood-streaked sputum—are of such general nature as to be almost useless. Close detailed history and thorough examination are usually not done because the patient does not appear to be acutely ill or when done, the few factors that lead to suspicion of undulant fever are overlooked and the case is diagnosed as "cryptogenic fever." The specific laboratory agglutination for undulant fever is overlooked when the Widal and agglutination for *Bacillus paratyphosus* A and B return negative. One should not hesitate to seek laboratory aid in the diagnosis of this condition. If blood is being sent to the laboratory for agglutination for the typhoid-dysentery group, agglutination with *Brucella* should also be requested. In the State health laboratory, many serums sent in for Wassermann and Kahn tests were titrated with *Brucella* organisms and were found positive in many instances in low titer. Persistent fever, profound sweats, leukopenia, undulant type of fever curve, should call for an agglutination test for undulant fever.

Conditions which may be confused with undulant fever unless definitely ruled out are typhoid, malaria, pulmonary tuberculosis, influenza, pneumonia, rheumatic fever, subacute bacterial endocarditis. The type of fever, absence of sweats, diarrhea, tympanites, toxic appearance, and demonstration of *Bacillus typhosus*, of *B. paratyphosus*, or positive Widal will differentiate typhoid fever. Tuberculosis has so many points of similarity that differential diagnosis will probably rest on laboratory results, especially the x-ray findings. The regularity of chills, fever, and sweat, response to quinine, and

demonstration of parasites in the blood will distinguish malaria. Influenza is a loose term applied to many respiratory conditions and appears often as a tentative diagnosis for undulant fever. The appearance of toxicity, with flushing and cyanosis of the neck and upper thorax, injection of the conjunctiva and congestion of the pharynx, rapid onset, increase in respiratory symptoms and short course will help to differentiate it. Pneumonia may at first be difficult, but absence of consolidation in the lobar type, and profound toxicity, rapid pulse, leukocytosis, and symptoms pointing directly to the respiratory tract will obviate confusion. Rheumatic fever can be differentiated by its acute onset and course, the tendency to affect more than one joint and its response to rest and salicylates. Subacute bacterial endocarditis may simulate undulant fever closely. Weakness, remitting fever, anemia, loss of weight are symptoms common to both. Sweating may occur in subacute bacterial endocarditis. An endocarditis may be caused by the *Brucella*. In undulant fever, when this does occur, differentiation will depend wholly on the results of blood counts, blood cultures and agglutination tests. Thus it is noted that undulant fever with its protean picture can be, and is confused with many diseases. In any patient suffering from a persistent fever, or from a persistent, minor, intractable upper respiratory condition with leukopenia, and palpable spleen, especially with relative lymphocytosis, the possibility of undulant fever should not be overlooked, and laboratory aid sought for positive diagnosis.

The points so far brought out may be illustrated by the following cases:

Case I.—S. S., white male, forty years of age, employed in the stock yards, was first seen July 30, 1934, complaining of fever of 102° F. for two days, chills, weakness, sweating, sore back and a feeling as of a steel band about the body, and inability to rest lying down. There was a recent weight loss. There was no history of sore throat, of malaria or of tuberculous contact. He gave a history of migraine. On further questioning it was determined that he drank unpasteurized milk at the stock yards.

On primary physical examination the only findings were a few râles in the upper left and lower left lung, and tonsillar debris. Examination was repeated on August 6th, at which time besides the lung findings there was a markedly enlarged and tender liver, palpable spleen and a persistent subicterus.

Examinations of urine and stool were negative. Urine culture showed

staphylococci. Blood count showed 3,880,000 red cells, 5700 leukocytes, 55 per cent hemoglobin, and a differential of 61 per cent polymorphonuclears, 27 per cent small and 6 per cent large lymphocytes, and 3 per cent transitional. Blood smear was negative for malarial parasites. Blood cultures were positive for *Brucella*. x-Ray of the chest showed prominent hilus infiltration. Wassermann and Kahn tests were negative. Agglutination tests were negative for *Bacillus typhosus* and *B. paratyphosus* on first examination, but positive, 1:100 for *B. paratyphosus* on September 15th, and later negative. Skin test for undulant fever was positive. Test for *Brucella* was positive 1:640.

A diagnosis of undulant fever and migraine was made, and the patient placed on symptomatic therapy, aspirin and quinine, for approximately one month with no alleviation of symptoms. On September 9th, 10 cc. of methylene blue was given intravenously; on September 12th, 5 cc. of methylene blue and gentian violet was given intravenously, and on September 15th, 10 cc. was given. The intravenous dyes caused marked reaction, but there was no apparent benefit from them. One week later, September 22nd, the serum of O'Neil was injected intravenously, 20 cc. the first day, 15 cc. the second and 10 cc. the third, a total of 50 cc. in three days. The patient became temperature free until October 1st, when a relapse occurred. He was again put on symptomatic therapy. Neosalvarsan was given on November 13th with no results. On November 16th the patient was transfused and from this point on became steadily better with loss of symptoms including the migraine.

Summary.—Because of the history of fever, chills, marked sweating, loss of weight and leukopenia and in the beginning, the absence of physical findings, blood was drawn for laboratory tests. The positive agglutinations, blood cultures and skin tests made the diagnosis positive. Treatment was based entirely on the response of the patient. Blood transfusion apparently was the deciding factor. It is noteworthy that in the control of the undulant fever the patient's migraine has cleared.

Case II.—J. K., white male, forty-five years of age, by occupation a farmer, was seen in August, 1936, complaining of hacking cough with expectoration of large amounts of blood-tinged sputum, fever of 103° to 104° F. and weekly chills. He also complained of profuse perspiration, fatigue, muscular aching, frequency of urination and nocturia. There was no history of tuberculosis or tuberculous contact or of malaria. He did drink unpasteurized milk.

Except for a few râles in the lungs and a palpable spleen the physical examination was negative. The urine showed a trace of albumin, the sputum was negative, and Wassermann and Kahn tests negative. Blood count showed 11,500 leukocytes, with a differential of 62 per cent polymorphonuclears, 25 per cent small and 7 per cent large lymphocytes, 3 per cent monocytes, and

demonstration of parasites in the blood will distinguish malaria. Influenza is a loose term applied to many respiratory conditions and appears often as a tentative diagnosis for undulant fever. The appearance of toxicity, with flushing and cyanosis of the neck and upper thorax, injection of the conjunctiva and congestion of the pharynx, rapid onset, increase in respiratory symptoms and short course will help to differentiate it. Pneumonia may at first be difficult, but absence of consolidation in the lobar type, and profound toxicity, rapid pulse, leukocytosis, and symptoms pointing directly to the respiratory tract will obviate confusion. Rheumatic fever can be differentiated by its acute onset and course, the tendency to affect more than one joint and its response to rest and salicylates. Subacute bacterial endocarditis may simulate undulant fever closely. Weakness, remitting fever, anemia, loss of weight are symptoms common to both. Sweating may occur in subacute bacterial endocarditis. An endocarditis may be caused by the *Brucella*. In undulant fever, when this does occur, differentiation will depend wholly on the results of blood counts, blood cultures and agglutination tests. Thus it is noted that undulant fever with its protean picture can be, and is confused with many diseases. In any patient suffering from a persistent fever, or from a persistent, minor, intractable upper respiratory condition with leukopenia, and palpable spleen, especially with relative lymphocytosis, the possibility of undulant fever should not be overlooked, and laboratory aid sought for positive diagnosis.

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A diagnosis of undulant fever and migraine was made, and the patient placed on symptomatic therapy, aspirin and quinine, for approximately one month with no alleviation of symptoms. On September 9th, 10 cc. of methocurochrome was given intravenously; on September 12th, 5 cc. of methocurochrome and gentian violet was given intravenously, and on September 15th, 10 cc. was given. The intravenous dyes caused marked reaction, but there was no apparent benefit from them. One week later, September 22nd, the serum of O'Neil was injected intravenously, 20 cc. the first day, 15 cc. the second and 10 cc. the third, a total of 50 cc. in three days. The patient became temperature free until October 1st, when a relapse occurred. He was again put on symptomatic therapy. Neosalvarsan was given on November 13th with no results. On November 16th the patient was transfused and from this point on became steadily better with loss of symptoms including the migraine.

Summary.—Because of the history of fever, chills, marked sweating, loss of weight and leukopenia and in the beginning, the absence of physical findings, blood was drawn for laboratory tests. The positive agglutinations, blood cultures and skin tests made the diagnosis positive. Treatment was based entirely on the response of the patient. Blood transfusion apparently was the deciding factor. It is noteworthy that in the control of the undulant fever the patient's migraine has cleared.

Case II.—J. K., white male, forty-five years of age, by occupation a farmer, was seen in August, 1936, complaining of hacking cough with expectoration of large amounts of blood-tinged sputum, fever of 103° to 104° F. and weekly chills. He also complained of profuse perspiration, fatigue, muscular aching, frequency of urination and nocturia. There was no history of tuberculosis or tuberculous contact or of malaria. He did drink unpasteurized milk.

Except for a few râles in the lungs and a palpable spleen the physical examination was negative. The urine showed a trace of albumin, the sputum was negative, and Wassermann and Kahn tests negative. Blood count showed 11,500 leukocytes, with a differential of 62 per cent polymorphonuclears, 25 per cent small and 7 per cent large lymphocytes, 3 per cent monocytes, and

1 per cent eosinophils. Blood smear was negative for malarial parasites. x-Ray of chest showed a marked increase in the density of the hilus glands. Agglutination tests were negative for *Bacillus typhosus*, *B. paratyphosus* A and B, but positive, 1:320, for *Brucella*.

The diagnosis was undulant fever. The patient was treated by a course of subcutaneous injections of vaccine. Following this he stated that the symptoms had subsided except the muscular aches. Urine at this time was negative, there was less density in the hilus areas, but slight fever still persisted.

Summary.—The suspicion of undulant fever in this case was based on the fever, chill and sweating, and was diagnosed on the results of laboratory tests. Malaria and tuberculosis had to be ruled out.

Case III.—A. T., colored housewife, twenty-six years of age, was admitted to the Cook County Hospital on September 4, 1935, with a diagnosis of suspected pyelitis. She complained of fever, chills and sweats coming on about noon, with an afternoon rise in temperature, frequency of urination and nocturia. No history of malaria and no tuberculous contact.

On physical examination the principal findings were increased bronchovesicular breath sounds over the right apex, palpable spleen, tenderness in right upper abdominal quadrant, and the liver palpable 1 fingerbreadth below the right costal margin. Urinalysis revealed albumin 1 + and a few pus cells. Stool and sputum examinations were negative. Blood count showed 3,230,000 red cells, 3250 leukocytes, 70 per cent hemoglobin and a differential count of 52 per cent polymorphonuclears, 42 per cent large lymphocytes, 5 per cent monocytes, and 1 per cent Turk cells. Blood smear was negative for malarial parasites. Blood culture gave a growth in subculture on Herrold media of pure culture of gram-negative cocci and bacilli. x-Ray of the chest showed increase in the right hilus markings. Urine and stool cultures were negative for typhoid-dysentery group. Agglutination tests were negative for *Bacillus typhosus*, but positive 1:1280 for the *Brucella* group (abortus).

The diagnosis was undulant fever. A vaccine was prepared at the University of Illinois and given in doses of 0.25 cc. (3 billion organisms per cubic centimeter) intramuscularly every three to four days. The temperature generally rose. On entrance (September 4th) it was 101.4° F., with a pulse rate of 124 and respiratory rate 26. On the 7th, temperature was 102.6° F., pulse 80, and respirations 20. Temperature then dropped. The vaccine therapy was continued and the patient felt so much better that she insisted upon leaving the hospital and was discharged on release, October 10, 1935.

Case IV.—E. J., a white male, thirty-five years of age, by occupation an acetylene welder, was admitted to the Cook County Hospital, March 15, 1935, with a diagnosis of lobar pneumonia. He became ill one month prior to admission with headache for one week and chest cold which persisted to date of entrance. He had a cough with scanty expectoration of grayish sputum, and

two weeks prior to admission a chill and fever lasting one week. He was anemic and had lost 35 pounds since the onset of the symptoms. Two weeks before admission he had a diarrhea, passing 3 or 4 stools a day, which persisted for one week, and nocturia twice nightly. History otherwise was negative.

On physical examination temperature was 104.5° F. (R), pulse 72, respirations 32, and blood pressure 116/80. Tongue was coated. Tactile fremitus was slightly increased in both lung bases, with dullness in the posterior lower one third of the thorax and moist râles throughout both lungs and scattered râles at the apices posteriorly. The abdomen was slightly distended and tympanitic, with slight tenderness in the lower half, and a questionable palpable spleen.

The impression was tuberculous pneumonia, tuberculous peritonitis, post typhoid, influenza and lobar pneumonia to be ruled out.

Urine, stools and sputum were negative. Wassermann test was negative. Urine and stool cultures were negative. Blood count showed 4,300,000 red cells, hemoglobin 90 per cent, 6250 leukocytes, with a differential of 46 per cent polymorphonuclears, 47 per cent large lymphocytes, and 7 per cent monocytes. x-Ray of the chest showed slight infiltration extending from the right hilum region. Blood smear was negative for malarial parasites. Agglutination tests were negative for *Bacillus typhosus*, but positive for *Brucella* through 1:1280.

The patient continued with a septic type of fever and profuse sweating. He was comfortable though listless and drowsy. The highest temperature was 104.8° F. Therapy was nonspecific, but followed generally the pneumonia routine. The patient was discharged on April 16th in good condition after a period of normal temperature.

SUMMARY

Undulant fever is a disease caused by infection with one of the specific types of *Brucella*, *melitensis*, *abortus* or *suis*. Clinically the condition is manifested by protracted fever, chills, sweats, possibly some upper respiratory symptoms, slow pulse, palpable liver and spleen, leukopenia, and loss of weight. The paucity of pathognomonic signs or symptoms makes clinical differentiation difficult. Recovery of the causative organism by blood culture, positive specific agglutination test, and positive skin test will make a positive diagnosis. Treatment is an individual problem both from the viewpoint of the physician and the response of the patient.

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SYMPOSIUM ON ALLERGY

The following clinics are included in this Symposium:

Russell L. Haden: ALLERGY AS A FACTOR IN GENERAL MEDICINE.

C. R. K. Johnston: INVESTIGATION OF THE PATIENT WITH ALLERGY.

W. Lorne Deeton: ALLERGY AS A FACTOR IN OTOLARYNGOLOGY.

A. D. Ruedemann: OCULAR MANIFESTATIONS OF ALLERGY.

E. N. Collins and Clark P. Pritchett: ALLERGY AS A FACTOR IN DISTURBANCES OF
THE GASTRO-INTESTINAL TRACT.

H. Scott Van Ordstrand and A. Carlton Ernstene: ALLERGIC BRONCHITIS.

C. L. Hartsock and F. J. McGurl: ALLERGY AS A FACTOR IN HEADACHE.

E. W. Netherton: ATOPIC DERMATITIS.

Richard S. Knowlton: BRONCHIAL ASTHMA: CAUSES AND TREATMENT.

C. R. K. Johnston: HAY FEVER.

George H. Curtis: CONTACT DERMATITIS.

ALLERGY AS A FACTOR IN GENERAL MEDICINE

RUSSELL L. HADEN

THE physician must know and treat many diseases. There are, however, very few fundamental factors or common denominators on which the production of these diseases depend. Thus, many infectious diseases are recognized, all of which depend finally on one common denominator, the action of a micro-organism. Other important fundamental factors are tumor growth, abnormalities of the internal secretions, and disturbances in nutrition.

Most disease, in the last analysis, is the result of chemical action in the body tissues. Bacterial injury is largely chemical from poisonous substances produced by the bacteria; endocrine and nutritional disturbances are entirely chemical. In considering all disease, it is just as important to evaluate the susceptibility of tissues to reaction as it is to recognize the agents immediately responsible for the reaction. The clinical picture represents the algebraic sum of the activity of inciting agents and the reactivity of the tissues. Thus an alteration in structure or function produced by some substance depends to a large extent on the susceptibility of the tissues concerned to the toxic agent. The great clinical variation observed in infectious diseases has long been recognized. With an equal dose of some specific causative organism, one individual may become very ill and another have relatively little trouble, due to differences in the reaction of the tissues to chemical substances produced by the invading organism.

Allergy belongs in the small group of common denominators of disease. The word designates a state of altered or abnormal reactivity of tissues to stimuli or allergens. This abnormal hypersusceptibility results in disturbances of structure or function of tissues peculiar to the affected individual,

when exposed to certain substances. The symptoms and signs of conditions due to the allergic state are almost entirely dependent on a spasm of smooth muscle and an alteration in the permeability of blood vessels which allows fluid to transude into tissues. There may be a hypersusceptibility to substances to which the normal individual is not sensitive at all or a reaction all out of proportion to the dose or toxicity of some substance to which a normal person does react. It is conservatively estimated that 10 per cent of all individuals show such hypersensitiveness so the allergic state must frequently be considered as a possible explanation for clinical phenomena.

Allergy is thought of especially in relation to a small group of diseases in which there is hypersensitiveness to ordinarily innocuous agents so that exposure to these substances produces marked spasm of smooth muscle and transudation of fluids into tissues. The classic examples are bronchial asthma in which spasm of the musculature of the bronchioles occurs, seasonal hay fever in which transudation of fluids from the nasal mucous membranes occurs in response to the irritation of pollen grains, hives, in which, as a result of changed permeability, fluids pass through the walls of the blood vessel into surrounding tissues with the production of a wheal. More recently, the group of true allergic diseases has been gradually enlarged to include at least some of other symptom-complexes such as migraine, epilepsy, spastic colon, perennial rhinitis, and cyclic vomiting. In most of this group, some agent or allergen which is harmless to nonallergic persons produces the symptoms.

Heightened susceptibility or allergy may also play an important part in the clinical picture of conditions due to agents which uniformly produce disease regardless of hypersensitiveness. Here we include the pathogenic bacteria. For instance, allergy is being considered more and more in evaluating the structural changes produced in tissues by the tubercle bacillus. Allergy must be thought of in a much wider group of clinical states than the so-called "allergic diseases." A person who is allergic to ordinarily harmless agents is apt to be more sensitive than normal to many or all toxic agents. This is well illustrated by the leukopenia due to amidopyrine often associated with ulceration of the throat (agranulocytic angina). Patients with this condition are almost uniformly allergic to

many substances. The bone marrow reacts abnormally to the drug because of hypersensitivity. Many similar examples could be cited.

This symposium has been prepared to stress the clinical importance of allergy in the production of human disease. Numerous diseases and conditions in which the hypersensitive state is the most important factor and the clinical picture resulting from the tissue reactions to allergens are illustrated. The altered reaction of the patient is the important fundamental factor since the offending substances produce no or less trouble in the nonsensitive individual. The wide variety of diseases and clinical conditions discussed in this group of papers emphasizes that allergy may concern every organ and almost every tissue of the body. The list could be greatly increased.

It would be most valuable to understand why a person becomes allergic and to be able to evaluate the fundamental chemical changes on which the hypersensitiveness depends. We know relatively little about basic factors entering into the acquirement of the hypersensitive state. The chemical changes which determine the altered tissue reactions must take place before a person can react abnormally to something to which he is exposed. Inheritance is most important. A person does not inherit hay fever but does inherit a chemical state which determines that he will acquire the hypersensitivity to pollen after being exposed to it. The allergic state can also be entirely acquired without apparent cause. The development of hypersensitiveness must be influenced by the level of metabolic activity, the state of the gastro-intestinal tract which determines the manner in which food is digested as well as absorbed, endocrine function, and the balance of the nervous mechanism. Time will certainly evaluate the rôle of influencing factors.

At present, the treatment of the allergic states is largely based on removal of contact with the offending allergens and specific desensitization. Not infrequently, however, the patient is hypersensitive to so many substances that specific removal or desensitization is impossible. Here the whole picture must depend on some fundamental alteration in the chemistry of tissues which might be amenable to treatment if known. The most logical approach would be to fundamentally change the

réactivity of tissues. This is dependent, however, on learning more about the chemical state on which allergy rests.

CONCLUSIONS

Allergy represents a most fundamental factor in the clinical picture of disease. It determines the type and degree of reaction to many substances which ordinarily do not produce disease as well as some pathogenic agents.

A person who is hypersensitive to one substance usually reacts abnormally to many since the allergic state represents altered tissue chemistry.

In almost every clinical problem, we must consider heightened susceptibility as a factor in the patient's disease.

It is just as important to evaluate factors influencing the allergic state as the hypersensitivity itself.

INVESTIGATION OF THE PATIENT WITH ALLERGY

C. R. K. JOHNSTON

THE diagnosis of most allergies presents no particular difficulty. In many cases, the patient or his friends have already determined the diagnosis and the allergist is consulted in an attempt to find the specific etiologic agent or agents, in order that relief may be obtained by eliminating these from the diet or environment. Therapeutic results depend largely on the degree of success in establishing these causative factors.

The importance of allergy, both to the general practitioner and the specialist, is rapidly becoming apparent. Various estimates reveal that from 7 to 10 per cent of the population suffer from one or more definite manifestations of allergy, while a much larger number of persons have experienced at some time in their lives a temporary or minor allergy which often is difficult to elicit except by careful questioning. Children form a large proportion of the allergist's practice.

The list of diseases due to allergy is still growing and the right of some for inclusion is open to question. None will dispute that true hay fever, allergic or vasomotor rhinitis, allergic bronchitis, and the great majority of asthmas are distinctly of an allergic nature. Probably most cases of migraine and many case of atopic eczema (especially in children), urticaria, and angioneurotic edema are due to food or some other allergen. The incidence of gastro-intestinal allergy is less definite, but it is probably common in childhood, especially in the form of cyclic vomiting, and it may be responsible for the occurrence in persons of any age of canker sores, "dyspepsia" (bloating, belching, epigastric distress, heartburn, etc.), anorexia, nausea and vomiting, diarrhea, mucous colitis, abdominal pain, and rarely bleeding from the gastro-intestinal tract, constipation, and pruritus ani. Claims are made that

some cases of epilepsy, purpura, erythema multiforme, Ménière's disease, and rarely dysmenorrhea and pain in the urinary tract can also be explained on a basis of allergy.

Confronted by a problem of doubtful etiology, we may apply certain diagnostic criteria. These are well summarized by Rackemann:¹

"1. A presenting symptom which can be explained by smooth muscle spasm or by increased capillary permeability.

"2. The occurrence of one or several other manifestations of allergy.

"3. A positive family history of allergy.

"4. The presence of positive skin tests.

"5. The presence of a blood eosinophilia."

The greater the number of the above characteristics that are present in a given case, the stronger is the indication that allergy must be considered as a factor in the patient's symptoms. The response to epinephrine furnishes a useful therapeutic guide in many cases.

Once it has been determined that the problem is of an allergic nature, the next step is to attempt to find the specific causative or exciting factor or factors. For this purpose, we have recourse not only to the usual methods of history, physical examination, and laboratory tests, but also to specific skin and other tests for allergens, therapeutic trial, and certain special examinations when indicated.

THE HISTORY

The value of a detailed history in problems of allergy is generally recognized. Swineford² says, "It is our belief that properly taken histories, properly evaluated, are of little less value than the more spectacular skin tests in the management of any large series of allergic manifestations." The necessity for determining the specific exciting factors must be constantly borne in mind while the patient is being questioned.

A knowledge of the mode and date of onset of the initial attack often yields valuable clues. If all the attacks are similar, the history of a typical one is sufficient, but frequently the sequence of events is helpful. It should be determined whether the attacks are seasonal or perennial as this is important in cases of rhinitis, bronchitis, and asthma. Many patients refer

to their nasal symptoms as "colds" and it sometimes requires careful study to determine whether these are true infections or recurring attacks of nasal allergy. The appearance of the mucous membranes during a typical attack readily differentiates the two; the pale, swollen turbinates of the patient with allergic rhinitis are in marked contrast to their inflamed appearance in cases of bacterial infection. The predominance of eosinophils in the nasal secretions also substantiates the diagnosis in cases of allergy.

The time of day when symptoms occur should be noted. The duration of the attacks, their frequency and severity, and the effect of medication also give further information. The degree of relief between attacks is of considerable prognostic value. Careful inquiry may reveal some precipitating or aggravating factors. Thus, an attack of asthma may follow an infection, such as a cold, or exposure to house dust, animal pets, the use of cosmetics, or ingestion of certain food. Climatic conditions such as moisture, dryness, or wind may be important and physical agents such as heat and cold may have some relation to the attacks.

The environment and occupation of the patient sometimes are responsible for the exciting factors. This can readily be appreciated in the case of a farmer, for example, whose contact with horses, dogs, chickens, cows, and grain dust presents a marked contrast with that of the beautician who comes in contact with orris root and tobacco fumes. Inquiry should be made as to the length of time the patient has resided in his present quarters and the effect of any recent change. The house furnishings demand special attention, particularly those of the bedroom, for about one third of a patient's lifetime is spent in that room. The presence of rugs and carpets, the type of bedding, the upholstery of the furniture, the curtains, toys, and unnecessary fixtures should be considered as possible allergens.

The effect on the patient's symptoms of a vacation or a change in habits or environment often furnishes a clue. A perennial rhinitis is frequently aggravated when a student returns to school in the fall or when hot-air heating is begun. The onset of hay fever or asthma may follow shortly after the patient has moved from one section of the country to another.

Migraine headaches, which were absent while the patient was on an extended vacation, may recur when he returns to his former work.

A history of any manifestation of allergy in the past should be carefully sought. Hay fever or perennial rhinitis frequently precedes the onset of asthma. When an adult with allergy presents himself for examination, inquiry must be made concerning a history of digestive upsets, eczema, or hives during childhood. If carefully analyzed, infections and colds may prove to be manifestations of a previous allergy. The history of operations, intercurrent infections, or hospitalization for any cause may be important. It is often observed that asthma is relieved for some time after a fever or a period of time in the hospital.

The general health of the patient deserves attention and a careful systemic review should be made. Inquiry regarding the usual symptoms of all the more common allergies should be made in an effort to elicit others which may be denied on direct questioning. The presence of anemia, hypometabolism, increased nervous tension, malnutrition, foci of infection, faulty dietary habits, menstrual irregularities, and inadequate rest are factors of importance that should be treated if one is to achieve the best results from therapy. A history of cough, headache, or constipation should lead one to question the patient regarding medications used for their relief, which may throw suspicion on drug sensitivity. Allergy to such widely used remedies as phenolphthalein and aspirin is probably more common than is generally supposed.

A positive family history of allergy forms a very useful criterion in doubtful cases, although a negative history is not of great significance. Investigation of the "family tree" should include four generations: the grandparents; the parents, uncles and aunts; brothers, sisters and cousins; children, nephews and nieces. The patient should be carefully questioned about each of the manifestations of allergy which may have occurred in any of these relatives. A family history of frequent "catarrh" should lead one to suspect allergic rhinitis. On the other hand, "eczema" may be used to refer to many types of skin lesions which are not classified as allergic dermatitis.

THE PHYSICAL EXAMINATION

Although most patients with allergy are otherwise healthy, one should never omit the physical examination. Patients frequently come to the clinic for only the "skin tests" or "food tests," but after the necessity for a thorough history and physical examination is explained to them, few fail to cooperate. Special attention should be directed to the eyes, nose, mouth, chest, and skin.

Careful search for areas of focal infection should be made, chiefly in the sinuses, teeth, tonsils, prostate, and bronchial tubes. A thorough examination of the heart is occasionally necessary to distinguish between cardiac and allergic asthma. Inspection of the optic disks is always indicated in cases of migraine, and at times a detailed neurological examination is necessary to exclude brain tumor or other organic lesions of the brain. Lastly, the general state of nutrition of the patient, nervous tension, evidence of low metabolism, etc., should be noted.

LABORATORY TESTS

All patients with allergy have the usual routine blood studies consisting of estimation of hemoglobin, red and white blood cell count with differential count, blood Wassermann and Kahn tests, determination of blood sugar, and urinalysis. Definite eosinophilia is further presumptive evidence of allergy. In cases where an element of infection is suspected, the erythrocyte sedimentation rate is of great value. Examination of the nasal secretion is often helpful in instances of doubtful nasal allergy. A predominance of eosinophils indicates allergy, whereas in true infections, neutrophils are largely found. The basal metabolic rate, gastric analysis, and additional studies of the blood chemistry are not infrequently indicated. In allergic bronchitis and asthma, a roentgenogram of the chest is made routinely. This is a necessary safeguard to exclude tuberculosis and bronchiectasis. Examinations of the sputum for tubercle bacilli are of course made in all doubtful cases, and autogenous vaccines may be made from sputum when the symptoms seem to be largely explainable on a basis of infection.

SKIN TESTS

Although skin tests are most valuable and have given impetus to the study of allergy, reliance on them alone is apt to be misleading. The diagnosis of allergy in most cases is made on the basis of the history and is confirmed by physical and laboratory findings, while the skin tests are performed mainly in an effort to determine the specific exciting agents. Frequently, we hear patients relate that they have had 20, 40 or more skin tests but "nothing was found." It must be emphasized, then, that if skin tests are to be made, they should be adequate to investigate thoroughly the particular allergy in question. Furthermore, a positive skin test does not always indicate that the patient is clinically sensitive to the allergen in question. Positive skin tests may reveal not only present sensitivity, but may be due to a sensitivity persisting from childhood or may represent a future sensitivity. Nor do completely negative tests always mean that the patient is not allergic. Finally, the size of the test is not necessarily correlated with degree of sensitivity.

The diagnosis of allergy having been made, skin tests are then resorted to in an attempt to determine the specific allergic factors. There has been much discussion regarding the relative merits of the scratch and intradermal methods of testing. Most allergists favor the intradermal method which, undoubtedly, is more sensitive. To secure the most satisfactory results, both methods must be used. In all cases of respiratory allergy we use scratch pollen tests, even though no seasonal variation of symptoms can be elicited. If sensitivity to pollen is established, tests for the epidermals and other inhalants and foods are usually completed by the scratch method. Where sensitivity to pollen is mild, however, the remainder of the tests can often be performed by the intradermal method, using dilute extracts where necessary. In cases of migraine, eczema, and other conditions where no sensitivity to pollen is present, all the tests are made intradermally.

The average patient is tested for reactions to the usual allergens of his environment and diet, making an average of from 150 to 180 tests. As a rule, the time required is about one hour on three separate days which need not necessarily be consecutive. Complete lists of these allergens for which tests

are made may be found in the various textbooks on this subject. In order to instruct his patient satisfactorily, the allergist must have considerable knowledge as to the source of these allergens in the patient's environment and diet and how they may be avoided. Extracts for testing must be properly prepared and, for intradermal testing, standardized as well. Such detail is beyond the scope of this article and for further information the reader is referred to the publication of Coca, Walzer and Thommen.³

Scratch tests are the safest and probably the best method for those who do few tests. We always use them in testing for pollens and also for inhalants and foods in highly sensitive patients. The back is the site chosen as it offers a large area for testing. Care must be taken, however, to wipe off the excess allergen if a reaction develops very rapidly. Constitutional reactions seldom occur if precautions are taken. When few tests are to be done, the forearm should be used as it undoubtedly is safer. The number of tests performed at one sitting depends largely upon the degree and number of reactions. Usually we are able to complete 60 to 80 tests, however. The technic of this and other tests mentioned is well described in the recent book by Louis Tuft.⁴

The intradermal tests are more sensitive and are used in all patients who do not exhibit sensitivity to pollen or possess a highly reactive type of skin (dermographism). Different dilutions of allergens are used, these being varied according to the reactions obtained and often patients showing moderate grades of pollen sensitivity can take dilute intradermal tests. Constitutional reactions may occur but are infrequent when the necessary precautions are observed. If the history indicates a high degree of sensitivity to any allergen, tests should be made either by the scratch method or with a very dilute solution intradermally, preferably on the arm. It is usually safe to do from 30 to 60 intradermal tests at one time.

Scratch tests are read in about twenty minutes and intradermal tests about ten minutes after completion. It is advisable to see all tests about three times, once before the time mentioned above and once after, in order to note any change that may take place. Certain standards for positive and negative reactions have been suggested, but experience is the chief requisite

for proper interpretation. Positive reactions are graded from one to four plus to represent the degree of reaction. The reactivity of the skin of different patients varies markedly and must be considered in all cases.

Patch tests have a very limited but useful field. In cases of contact dermatitis, where an external irritant is the etiologic agent, they are the only tests of value. The test is extremely simple. The suspected agent is applied to the skin of the arm or back on a small square of cloth and moistened with distilled water if necessary. This is covered with a piece of cellophane and held in place by adhesive tape or by bandaging, if the patient is sensitive to adhesive. The reaction is observed usually in twenty-four hours and a positive reaction reproduces, more or less, the original lesion.

OTHER TESTS FOR ALLERGENS

Ophthalmic and nasal tests are seldom used, chiefly because they are annoying and uncomfortable to the patient and because the previously mentioned tests are reliable. The eye test is useful prior to the administration of horse serum. The nasal test is employed in the rare cases of patients with hay fever who have negative skin tests.

The passive transfer method of testing (indirect method) is extremely useful and has a widespread application. It is indicated in children too young for direct tests, in cases of severe eczema, hives, or other conditions where suitable areas on the skin are not available, in all acutely ill patients, and in patients whose skin is so highly sensitive as to make accurate interpretation of direct tests difficult. A nonallergic volunteer is used and test sites are made on his back by injecting the patient's blood serum. After a lapse of forty-eight hours, these sensitized sites are tested by the intradermal method. Usually group tests are made and later the individual members tested in the group that showed reactions.

ELIMINATION TESTS AND THERAPEUTIC TRIAL

In some cases where allergy is suspected, especially in the case of foods and where skin tests have been negative or for some reason cannot be performed, Rowe has advocated the use of elimination diets. If symptoms disappear, the suspected agent should again be added to the diet and proof of the signifi-

cance of this agent is shown if the symptoms recur. This method may be used to confirm the significance of various inhalant allergens after symptoms have been relieved by excluding it from the environment of the patient. An excellent example is the recurrence of symptoms of hay fever when the patient returns from a vacation spent in a region free from inciting pollens.

SPECIAL EXAMINATIONS

A roentgenogram of the chest should be made routinely in all cases of asthma and allergic bronchitis in order to exclude the possible presence of tuberculosis or bronchiectasis. In all cases of respiratory allergy, a thorough examination of the nose and throat is indicated to detect possible foci of infection, deviated nasal septa, polyps, spurs, or other physical barriers. Roentgenograms of the sinuses and teeth are of great value in many cases. Instillation of lipiodol may be necessary at times to exclude bronchiectasis, and bronchoscopy is also occasionally used. In cases of suspected gastro-intestinal allergy, a complete roentgen examination of the gastro-intestinal tract is at times valuable in excluding organic disease. Gallstones or a poorly functioning gallbladder may be the precipitating factor in some cases of hives. Lastly, the leukopenic index is very useful as an aid in diagnosis of food allergy where the skin test was doubtful or a false positive or negative reaction suspected.

SUMMARY

The procedure used in the investigation of allergy has been outlined. Emphasis has been placed on the importance of a thorough history to establish the diagnosis of allergy, confirmation of which is obtained by the physical findings, laboratory tests, and certain special examinations. Skin tests are of great value in the search for the specific etiologic factors and in doubtful cases to add further presumptive evidence of allergy.

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ALLERGY AS A FACTOR IN OTOLARYNGOLOGY

W. LORNE DEETON

MUCH information has been gained regarding the relationship between allergy and otolaryngology in the last few years. About seven years ago, I analyzed a series of patients with allergy and found that in only about 50 per cent had investigation and treatment given relief. At present, I do not think it is exaggeration to state that we are able to help from 85 to 90 per cent of these patients. Part of this increase in good results is due to improved technic in performing the tests, and part is due to our increasing knowledge of this still unsolved problem. This increase in knowledge has been brought about largely through a more unselfish cooperation of the internist, the allergist, and the otolaryngologist.

Many observers have stated that approximately one third of all the patients seen in a general practice complain of some nasal trouble. Of these, well over 50 per cent will be found to have allergic rhinitis.

The symptoms of allergy are so varied that they enter all the phases of our profession. Too often the rhinologist does not refer a patient suspected of having allergy to the allergist, fearing that the patient would be subjected to a long series of weekly injections or, what is more, would probably never come back to him for observation. On the other hand, many allergists have learned to use the head mirror and nasal speculum and have preferred to examine their own patients, fearing that if the rhinologist saw the patient a series of perhaps unnecessary and discouraging nasal operations would be instituted. The allergist is not too enthusiastic about sinus surgery as it has been practiced in the past.

The symptoms of allergy are many and varied. The commoner ones include nasal trouble, asthma, bronchitis, hives,

hay fever, eczema, so-called "migraine headaches," conjunctivitis, mucous colitis, indigestion with gas, angioneurotic edema, drug sensitiveness, and contact dermatitis. Recently I have come to believe that many cases of Ménière's disease are due to allergy, probably being caused by some edema in the labyrinth. Within the last two years, we have been accumulating data on this subject after examination of patients referred from the neurological and medical departments of the Clinic. A great many of these patients are found to have a lowered basal metabolic rate or some other endocrine deficiency or imbalance.

The commonest symptoms which cause these patients to seek advice of the rhinologist are a nasal or postnasal discharge, nasal obstruction, headaches, and sneezing.

When the patients with nasal symptoms enter the office of the ear, nose and throat man, one of their great fears is that they are going to be told that they have sinus trouble. The laity, and I am afraid many physicians, believe that if sinus trouble is found it probably means an operation followed perhaps by others—a most fatalistic outlook.

With the increasing knowledge of allergy during the last few years, the amount of sinus surgery has decreased enormously. A more thorough history and general examination of these patients have also been partly responsible for this decrease.

In examining a patient suspected of having allergy, a very detailed history should first be elicited. The importance of the family history has been discussed elsewhere in this symposium as have food idiosyncrasies.

After a careful history has been elicited, the examination is very simple. The appearance of the turbinates and mucous membranes is generally rather typical in the presence of allergy. They usually appear pale and edematous and some thin, watery secretion can often be seen. The turbinates are not always this pale color, but occasionally they may appear quite pink and irritated. On examination of the nasopharynx, the posterior ends are often seen to be pale and swollen, and at times they completely fill it. On transillumination of the sinuses, one or more are frequently found to be dim or dark. At this stage of the examination, if there is still any element of doubt about transillumination, roentgen examination can

be made, although this is not necessary in every case. If one suspects the presence of a thickened polypoid membrane in one of the sinuses or a polyp, lipiodol can be injected into the sinuses, this being done according to the methods described by Proetz. We prefer that these methods be used in cases where it is desirable to determine whether a sinus is normal. *i. e.*, whether the sinus fills completely or whether the dimness is due merely to a small or narrow sinus. Of course the density of the bone is also a factor in transillumination. Previous operations on a sinus may present a problem in the interpretation of roentgen films, and here the use of lipiodol is often of great assistance.

The membranes of the sinuses are continuous with those of the nose and are of the same structure—ciliated columnar epithelium, containing many mucous glands. In an allergic nose, the membranes lining some of the sinuses can become so thick and polypoid as to completely fill them. Hence, one can easily see how, if superimposed infection follows an acute coryza in such a maxillary sinus shall we say, it has no chance to fight the infection. The membrane is waterlogged, has a poor blood supply, and the cilia have ceased to function.

In the past, a patient who had an antrum with a reputed thickened membrane was much too frequently subjected to operation. One reads and hears a great deal about hyperplastic ethmoiditis. It is my belief that most of these cases are due to allergy, and treatment outlined along that line secures a good result. Certainly surgery alone will not cure such cases. Perhaps some surgery may help in giving partial relief from symptoms, but the original cause of the trouble must also be removed if the patient is to be entirely satisfied with the result.

If these patients are studied from the viewpoint of allergy as well as rhinology, it is remarkable what conservative management can do. The elimination of the offending proteins will lead to a healthier mucous membrane. The cilia may return to action, and the sinus may clear itself by a natural process. This restoration can be speeded up by occasional irrigations of the sinuses. In washing the maxillary sinuses, we prefer to wash through the natural ostium since the patients much prefer this method. By use of this method, the patient does not feel that cracking of bone, and furthermore, there is no pain.

The country is full of "sinus patients" who have made the rounds from surgeon to surgeon, submitting themselves to repeated operations without relief. These are the patients who spread the news that "once a sinus, always a sinus." They usually end up as psychoneurotic problems. More careful study of such patients on the first examination might have salvaged them and it certainly would have saved them years of misery and the family a great deal of financial distress.

During this past summer, I saw a woman who had had fourteen operations upon the sinuses; the turbinates had been removed and openings made into all the sinuses. She was practically a nervous wreck and made those who lived with her miserable. She gave a perfect history of allergy and skin tests revealed a four plus reaction to orris root. Another man who had undergone eleven operations was found to have a very severe reaction to feathers. Another patient, if his story can be credited, claimed that he had had forty-four nasal operations.

Another group of patients frequently seen by the rhinologist is comprised of those who have had polypi removed from the nose on one or many occasions. The mucous transparent polypi are, I am quite convinced, almost if not always due to allergy. Unless the cause for their formation is removed, they will almost invariably return. The secretions from an allergic nose, when placed on a glass slide and stained, usually show many eosinophils. These may frequently be difficult to demonstrate since these eosinophils are often in a degenerated stage, and the cherry red granules may not show up very well with the stain. Nasal polypi and the swollen, allergic, mucous membrane also show many eosinophils and plasma cells.

In these patients whose noses are full of polypi, it is often necessary to remove the polypi even while a regimen for the elimination of allergens is being carried out in order to give sufficient breathing space. All the polyps need not be taken out at once. Frequently, after their complete removal, one is surprised to find a few days later another polyp in each side. These usually have dropped down from higher up after removal of those below. In many of these patients it is necessary to do a submucous resection later in order to secure good ventilation in the nose and allow proper aeration of the sinuses.

We do not advocate the removal of the turbinates. Once

a turbinate has been removed, the normal physiology of the nose has been disturbed. These important structures are built so as to catch the incoming air and whirl it in currents, thus delaying its passage to the lungs. This allows the air to become warm and moistened before reaching the lungs. The turbinates act normally as the coils of a radiator and, having a rich blood supply, help to warm the air. The mucous glands in the mucosa of the turbinates secrete mucus to moisten the air. Thus it is seen that the turbinates perform a threefold function.

During the last few years, one has heard a great deal about the ionization treatment of the allergic nose. Various combinations of metals have been used, one of the most popular consisting of a solution containing zinc, tin, and cadmium. One electrical pole is placed in each nostril and the nostrils are then carefully and tightly packed with pieces of gauze soaked in the solution. An electrical current is run through the patient for fifteen or twenty minutes. We used this form of treatment in a series of selected volunteer patients and our results were practically nil. Many patients seem willing to try these short cuts to relief but there are no short cuts for these complicated cases of nasal disturbances associated with allergy. Only the closest cooperation of the internist, allergist, and rhinologist will give the patient the relief and comfort that he seeks when first he comes for consultation.

OCULAR MANIFESTATIONS OF ALLERGY

A. D. RUEDEMANN

THE ocular manifestations of allergy may involve any portion of the eyeball or orbit, although some parts may not be as severely involved as others. As more complete studies of patients are made, more cases of allergy are found to occur in the group of ocular diseases and more patients find relief following treatment for their allergy as they do the removal of foci of infection or any other form of treatment.

Probably the most common cause of ocular allergy is face powder, and this is followed by other cosmetics; then come the local agents used for hair wash and other cosmetic preparations which are used mostly by women. These produce a purely local sensitivity—so-called “contact dermatitis”—and elimination of the face powder, rouge, or face cream, and restriction of their further use will clear up the local condition and make the patient comfortable. However, there is a group of patients who have a local sensitivity to some of these substances in addition to an underlying general sensitivity that is the basis for their trouble. In each case of local dermatitis, it is advisable to make patch tests for all cosmetics and drugs the patient uses and to eliminate the use of any substance which gives a positive reaction. For edema of the lids and fine silver scaling on the margins of the eyelids, these patients must use some substance to which they are not sensitive or use nothing except cold, dry compresses. Cases of blepharitis marginalis sicca often fall into this group; however, they usually are due to a general sensitivity caused by foods and, in these cases, an entirely different approach of investigation must be used. This includes determination of allergens as well as examination to determine the presence of any foci of infection. In addition, it is wise to determine whether they are sensitive to any bacteria, especially the staphylococci.

Recurring chalazia are best handled by checking the refractive error and muscle balance and then, if they tend to recur after the refractive error has been properly corrected, tests for allergy should be made and a careful regimen for elimination of allergens instituted in accordance with the results of the tests. Here, again, some general condition rather than a local irritant is usually the cause, and unless the general condition is corrected chalazia will tend to recur.

Recurring styes fall into the group of conditions due to bacterial sensitivity. Usually the staphylococcus is the offending bacterium and, in addition to tests for the bacterials, allergens should be investigated if the autogenous staphylococcus vaccine does not tend to give relief.

At the present time, the part of the eye most frequently involved by allergy is the *conjunctiva*. Both the ocular and the palpebral conjunctiva may be involved in a reaction which is due to some substance to which the patient is sensitive. The first problem must be the elimination of purely local irritants that fall in the same group as external irritants or so-called "contact dermatitis." When the sensitivity is due to some transitory process, such as paint with its turpentine or the use of dusting powders, the condition will clear up when that substance is eliminated. The appearance of the palpebral conjunctiva in such instances is that of a very low-grade, edematous reaction in which the conjunctiva is slightly hyperemic, small pinpoint-like granules being seen over the entire lower surface of the lower lid and the patient has the feeling that sharp, needle-pointed foreign bodies are cutting across the cornea when the eyeball is moved. The best local treatment for these patients is the application of cold compresses and adrenalin if they are not sensitive to the adrenalin. It is unwise to submit these patients to general studies for determination of allergens on the first appearance of a conjunctivitis. However, if it tends to recur on the least provocation or if there is a recurrence of the previous conjunctivitis, it is wise to make these examinations in order to rule out the possibility that some other substance is causing the underlying condition which makes the ocular conjunctiva so extremely sensitive.

The greatest amount of study in conjunctivitis due to allergy has been directed to the so-called *vernal conjunctivitis*

or "spring catarrh." In 1923, Townsend called attention to the frequency of vernal catarrh in patients with hay fever. Lehrfeld of Philadelphia and others have contributed greatly to this field of study. In our experience vernal catarrh has been, in most instances, due to some allergen. Not infrequently this conjunctivitis appears in the spring during the season of the tree pollens and is carried forward by other reactions to pollens. It is very difficult in most instances to determine the pollen that causes vernal conjunctivitis. However, by careful study and rechecking, the substance that is causing this tremendous reaction in the lid will be found. We have found that the best treatment for local relief has been the use of cold compresses, adrenalin, and mild anesthetic substances to prevent the patient from rubbing the eyes too severely. During this stage of severe inflammation, however, it is better to use radium, if possible, in order to shrink down the large granular masses and give the patient some relief. There is little or no danger connected with a vernal conjunctivitis insofar as the eyesight is concerned. There is a tremendous amount of discomfort, however, and the patient is unable to carry on his work because of the marked photophobia, lacrimation, and blepharospasm. Scraping of the lids has not been successful in our hands for the simple reason that the reaction has been great and we feel that the use of radium is much more satisfactory.

The minute granular reaction of the lids is usually due to sensitivity to some food which should be eliminated following careful study. In some instances, a contact dermatitis may be the etiologic factor, and further study should be made to determine any possible causative substances in the home or place of work.

The *bulbar conjunctiva* is frequently involved in a chemical conjunctivitis as well as in other types of contact conjunctivitis and here, again, the history of the patient must be carefully worked out and a study made of his daily activities and surroundings.

Except in a very few instances, involvement of the *cornea* is usually due to some general allergic condition and not to any local, so-called "contact dermatitis." However, our most outstanding case of corneal involvement was in a girl who had a serious corneal desquamation in each eye. It was found that

she was extremely sensitive to orris root and only to orris root. Elimination of this substance from her daily routine produced complete relief and she has not had a recurrence of the process.

Conjunctivitis associated with *keratitis* is usually due to a general process. In every instance of keratoconjunctivitis and phlyctenular keratoconjunctivitis, a study for allergy should be made as well as investigation to determine whether it is a tuberculous process. In many of the patients with phlyctenular keratoconjunctivitis, the process is caused by an underlying food sensitivity and, unless this is eliminated, there will be recurrences of the condition with scarring of the cornea. It is my belief that in no instance should the patient be given tuberculin therapy or any other treatment for tuberculosis unless the possibility of food allergy has been carefully checked. It has been our experience that some of those patients with questionable tuberculosis have been relieved by the administration of a diet high in vitamins, including one or two quarts of milk every day and one of the fish oils. In several of these patients there has been a sensitivity to the fish oils or milk or some other food, and I believe that this has definitely made their eye condition worse. Milk is not a substance that anyone with allergy can take without careful study. Many of the youngsters have sensitivity to milk in which case it must be definitely eliminated from the diet and another food substituted.

The involvement of the cornea ranges from a very fine punctate-like keratitis to the involvement of the entire cornea in one large corneal desquamation. At first, the superficial epithelium of the cornea is involved but, as the process continues, there is a deep interstitial involvement with permanent scarring. It is, therefore, important that these patients be handled carefully and submitted to a careful study early and then they will obtain a good visual result as well as relief from the photophobia, lacrimation, and blepharospasm. If the process is prolonged and recurrences take place, interstitial vascularity occurs, resulting in permanent scarring with definite loss of vision. In conjunction with the keratitis, there may be a secondary iritis. The pupil must be kept well dilated with atropine, scopolamine, duboisine, or some other substance to which the patient is not sensitive. It is important that this warning be given here because of the marked sensitivity these

people have to the alkaloids, atropine being a very prominent one and the patient, under no circumstances, should use atropine if sensitivity exists, as it will add to his discomfort and increase the local irritation. This is also important in the use of other substances around the eye in people who have a definite sensitivity.

Once the diagnosis of allergy is made, no substance should be placed in the eye unless one is absolutely certain that the patient is not sensitive to it. It is not difficult to make patch tests and in most instances these patients will be much more comfortable without the instillation of any drugs, using dry, cold compresses and some adrenalin, if the patient is not sensitive to the adrenalin itself. In this regard, one must be very careful in using the mild anesthetics that are employed commonly around the eyes. Some are extremely irritating to patients who have a sensitivity and again, unless one is careful, the eye may become involved in a marked desquamation with secondary scarring. Wherever there is a corneal desquamation due to sensitivity, it is wise to cover the eye with an eye pad or some cover in order to eliminate the sensitivity to light as most of the patients with keratoconjunctivitis have a marked sensitivity to light. Once the offending substance is eliminated, a good recovery is usually made, providing the treatment has not been too severe. Silver nitrate and other irritating substances must not be used if good results are to be obtained.

We have not encountered involvement of the deeper corneal structures except secondary to long-standing, recurring, superficial involvement. However, it is quite possible that some of the deeper structures may be involved in an allergic type of reaction. Excessive lacrimation due to hyperactivity of the gland is usually a secondary manifestation, being due to the irritation of the conjunctiva rather than to the true sensitivity of the gland. However, in three instances, we have been unable to find any change in the lids except that due to the marked lacrimation. Two of these patients have had deep radiation therapy to the lacrimal gland with success; the other has been treated in the same manner but without success.

The iris is not an uncommon seat of allergic reaction. This type of iritis is not serious and is of a mild form but it is painful due to the light stimulus. In two of our cases, the

iritis occurred during the hay fever season while the patient was having an extreme reaction due to a pollen. Dilatation of the pupil with atropine and hot compresses are indicated in this group because of the irritation accompanying the involvement of the iris. The patient should not use the eyes and care must be exercised to control the allergy in general.

Changes in the lens are found as a secondary manifestation and, in some instances, they are probably due to the allergy. Recently, we operated upon two patients for removal of cataract. Both were young girls under twenty years of age, in whom marked lens changes had developed due to an eczematous condition. The purely individual sensitivity to a drug is shown by those patients who have dinitrophenol cataract. In contrast, compare the number of people who use the substance, while only a small number of them develop cataracts. However, in spite of the fact that the number is small, no one should use this substance because the tendency for cataract to develop cannot be ascertained before the drug is employed. Development of changes in the lens in these patients occurs slowly and may appear even six to nine months after use of the substance has been discontinued.

All our patients with vitreous opacities are studied carefully to determine foci of infection and, in addition, studies to determine food allergens are made. It is not unusual to find that these patients have a marked sensitivity and, although the floating vitreous opacities do not disappear, they do not increase in number. If the patient adheres to the diet, he is made much more comfortable because, in conjunction with the vitreous opacities, there is slight irritation and some photophobia. If these patients are studied carefully, it is found that they do have a slight hyperemia of both disks and the retina. The margins of the disk are hazy and the entire disk is reddened.

The disks and retina are involved in allergy as frequently as any other part of the eye. A local wheal may involve the nerve head, showing a definite papilledema of 2, 3, 4, or more diopters, which is definitely due to an allergic reaction. We have several patients who can produce edema of the disk if they violate their diets and indulge in substances to which they are extremely sensitive. This is also true of some of the so-

called "cases" of retrobulbar neuritis. These patients evidently have a retrobulbar edema of the nerve but, by a careful study and elimination of allergens, recovery of the use of the eye is made. It is my opinion that no patient with nerve head involvement, for which no clear-cut etiological factor has been found, should go without complete investigation of allergy.

Patients with so-called *toxic neuritis* due to a definite sensitivity to a certain substance may also be sensitive to other substances which, over a period of time, produce low-grade irritation of the disk and secondary optic atrophy. Secondary atrophy of the nerve heads and other allied conditions may also be produced by continued general sensitivities extending over a long period of time.

It is more difficult to determine the part played by allergy in a *chorioretinitis* or *retinitis* than in any other part of the eye. At the present time, we have only a small group of patients in whom we believe the problem is definitely one of sensitivity. However, better permanent results will be obtained in these patients who have an irritation of the retina due to an infection in the tonsils or teeth if the infected area is swabbed and the material used for culture. Then a vaccine should be made and the patient given the vaccine over a long period of time after the focus of infection has been removed.

In the last five years, we have been making a very interesting study on patients with myopia and keratoconus. These patients have been studied from every point of view including the possibilities of glandular involvement as well as for foci of infection. In going over the records we have found that each and every one of them has a very definite sensitivity. In some cases this is not as marked as in others, but each has a positive reaction to some substances, mainly the foods. It is not unusual to find that the younger patients with myopia have sensitivities to milk, butter, eggs, and chocolate, whereas, in the older group, they tend to have a reaction to pollen as well. In this study, more than a hundred patients have had definitely positive reactions to one or more substances and, by the elimination of these substances, we feel that the myopia tends to be less progressive and, in some cases, not to progress at all. Sufficient time has not elapsed for a definite statement to be made that myopia is due to allergy but the large number

of patients who have myopia and are sensitive, and the fact that the sensitivity seems to go along with the development of the myopia would seem to substantiate this belief.

Patients who have keratoconus tend to have a higher ratio of sensitivities than do those with myopia. We have not yet attempted to type the various cases of myopia but this probably will be done in the near future. In some patients, we have been able to follow the course of the myopia through the seasons of their worst pollen allergy and have found that the greatest change occurred during that period in which the general body sensitivity was at its height. We have handled these patients by making careful refractions, prescribing well-regulated diets, and substituting for the foods that are eliminated other substances such as dicalcium phosphate, vitamins A, B, and D, as necessary. Here again, care must be exercised to determine that the patient is not sensitive to milk and cod liver oil. As time elapses, further reports will be made on this clinical study but, to date, it must be said that the possibility that allergy plays a part in the development of myopia is very strong.

I have seen one patient with *exophthalmos* due to edema of the orbit. The entire orbital tissue was edematous and the eyeball was proptosed to a slight extent. Edema of the lids is not uncommon in allergy, especially of the lower lids, and the so-called "morning edema" of the lids is probably due to a feather pillow or some other substance with which the patient has been in contact.

Patients who have ocular manifestations of allergy usually present similar pictures. The process is irritative and chronic, tending to recur over a period of years. Periods of remission may extend from six months to several years. A careful survey of these patients is very important because, if the process can be arrested, the eyeball is usually restored to normal condition with little or no sequelae. If, however, recurrences are numerous, the tendency to formation of secondary scar tissue follows with permanent damage.

Allergy does not explain all the conditions around the eyes. However, in patients who suffer from recurring eye lesions and when foci of infection including the cervix and prostate have been searched for and removed, bacterial as well as general

allergy should be considered. It may be that the allergic response to the bacteria is causing the eye condition. However, if all foci have been removed and they no longer present any possibility of infection, allergy must be considered and a careful study of the general condition made. Careful history and a thorough physical examination must be included.

A patient on a diet for the elimination of allergens may not get well for the reason that he does not adhere to the dietary regimen. Some local treatment is indicated in order to draw attention to the fact that he must be careful regarding the use of his eyes and that he must continue to follow his diet in order to take care of the local condition. In most instances, it is wise not to subject the patient to very irritating substances because the patients with sensitivities are usually sensitive to most of the drugs and medicines. Most of the patients who have allergy will not be reluctant to have a complete study as they have had the process over such a long period of time that they will be willing to have anything done in the hope of securing some relief. However, after treatment of allergy for at least three months, without any results, it might be wise to repeat the entire examination in order to ascertain whether or not some etiologic factor might have been overlooked.

It is my opinion that, as we study these patients more and more from the point of view of general systemic involvement, we will eliminate many of the patients with the so-called "idiopathic conditions." The field is still undeveloped and offers an excellent territory for research and clinical study.

ALLERGY AS A FACTOR IN DISTURBANCES OF THE GASTRO-INTESTINAL TRACT

E. N. COLLINS AND CLARK P. PRITCHETT

THAT allergy may be a causative factor in disturbances of the gastro-intestinal tract has been definitely established, but controversy exists relative to the frequency with which this factor is encountered. When dealing with gastro-intestinal problems, the indications for investigation of allergy have not been clearly defined. Hinnant¹ has reviewed our experiences in gastro-intestinal allergy from the viewpoint of the allergist. This discussion is written from the standpoint of the gastro-enterologist and will attempt to answer the question, "When is allergy likely to be the cause of the patient's digestive disorder?"

All physicians have had patients who experienced remarkable relief of symptoms simply by the elimination from the diet of one or more foods. Problems in allergy are encountered by every physician, regardless of his primary interest, and gastro-enterologists have found that it is important to consider allergy in the history of each patient's past and present illness, as well as to inquire whether there is a family history of allergy. In our experience, allergy has been of significance not only in certain functional disturbances of the gastro-intestinal tract, but it has proved important as an aggravating factor in certain ulcerative processes, such as ulcerative colitis, when the patient definitely is an allergic individual.

However, our experience leads us to believe that allergy as a factor in these disturbances is overemphasized in the literature at the present time. Adequate investigation for allergy involves considerable time and effort. Before starting this investigation, due consideration should be given to obvious neurogenic and constitutional factors, irregular habits of living, the ingestion of well known mechanical and chemical irritants to the gastro-intestinal tract, improper bowel habits, and other possible causes.

Certain present-day enthusiasts would have us believe that all functional and some organic disturbances of the gastro-intestinal tract are due to allergy. At the same time, it should be more generally known that gastro-enterologists are seeing patients who have had skin tests and other examinations for allergy and who have followed regimens for the elimination of allergens, not only without relief of symptoms but evidence of marked malnutrition has developed.

Kantor² states that, from his experience in gastro-enterology, "in not much over 1 per cent of patients was the allergic factor very important." Thus, it is apparent that the incidence of gastro-intestinal allergy is not yet established.

Skin tests as a means of determining food allergy have not proved reliable in 100 per cent of the cases. At the present time, the consensus of opinion is that they are reliable in not more than 50 to 65 per cent of the cases. All workers in this field admit that a positive reaction does not mean that that particular allergen is of clinical importance at the time of the examination, nor does a negative reaction necessarily indicate that that particular allergen is excluded as a possible cause.

The terms "food allergy" and "gastro-intestinal allergy" are not synonymous. We prefer to limit the term "gastro-intestinal allergy" to the manifestations of reactions due to allergy that are limited to the alimentary tract, and the term "food allergy" to include all the manifestations of allergy due to foods; these may be respiratory, cerebral, or cutaneous, as well as gastro-intestinal. Allergists emphasize the fact of *multiple sensitization* in allergy. In most of our patients who had gastro-intestinal symptoms due to allergy, there were manifestations of allergy elsewhere in the body, such as perennial allergic rhinitis, migraine, hay fever, or asthma. These patients had gastro-intestinal allergy, but they also had respiratory allergy or cerebral allergy and both were due to food allergy.

The diagnosis of food allergy with gastro-intestinal manifestations is largely a matter of exclusion. When evidence of organic disease has been excluded by the use of complete clinical, roentgenological, and laboratory examinations, allergy should be suspected as a cause of digestive symptoms if one or more of the following features are present:

1. A family history of allergy.
2. Proved allergy elsewhere in the body or symptoms in many organs, some or all of which could be attributed to allergy.
3. Presence of gastro-intestinal symptoms for a number of years, sometimes many years, and particularly if they date back to early childhood or if there is a history of other evidence of allergy during childhood.
4. No evidence of any marked detrimental effects on the general health although these symptoms have been present for many years.
5. Marked variability of symptoms in regard to character, location, duration, and time of onset. They may occur in cycles or may be present daily. The less characteristic they are of organic disease and the usual functional gastro-intestinal disturbances, the more one should think of the possibility of allergy as the cause.
6. Failure to improve following adequate management without regard to allergy.
7. History of definite food likes or dislikes.
8. Production of gastro-intestinal symptoms by repeated ingestion of a particular food. This makes it likely that other foods offend to a lesser or greater degree.
9. Absence of symptoms when suspected foods are eliminated. Reproduction of symptoms by ingestion of suspected food.
10. Normal sedimentation rate of erythrocytes suggesting that malignant or infectious disease is not present.

COMMON NONALLERGIC CAUSES OF FUNCTIONAL INDIGESTION

At least 50 per cent of patients who consult the gastroenterologist have functional disturbances of the digestive tract. These are commonly due to various neurogenic or constitutional factors, including anomalies and improper habits of living, such as irregular hours, inadequate rest, too much "roughage" in the diet, and particularly improper bowel habits such as the use of irritating cathartics or enemas over a long period of time. We do not believe all these factors should be included under the general heading of "neurosis." In our experience, irregular habits of living and unphysiologic bowel habits are the commonest causes of functional disturbances of the gastro-intestinal

tract. When the neurogenic feature is prominent, patients often experience relief of symptoms when complete clinical, roentgenological, and laboratory examinations assure them of the absence of organic disease.

An analysis of many of the case records wherein relief of symptoms was attributed to the elimination of allergens has revealed the fact that these patients not only had reassurance that no organic disease was present but they also had excellent nonallergic management. This naturally raises the question as to which part of the treatment should receive the credit. Later, many of these patients disregarded food allergy without suffering any ill effects. In these instances the allergists remind us that the factor of food allergy cannot be positively excluded because a tolerance might have been established in the meantime.

SYMPTOMS OF GASTRO-INTESTINAL ALLERGY

There are no characteristic symptoms of gastro-intestinal allergy. Many persons have gastro-intestinal symptoms due to the ingestion of some foods with which they come in contact *occasionally*. Such patients usually are able to recognize that the symptoms are caused by this food and avoid it thereafter. This is the "fortunate allergy" of Vaughan,³ in that it need cause concern to neither the patient nor the doctor. However, this type of reaction may give one a lead that a major allergy or "unfortunate allergy" is present.

The patient with "unfortunate allergy" is usually sensitive to some allergen with which he comes in contact daily or very frequently and hence is unable to recognize it as a cause of his symptoms.

An analysis of 100 consecutive cases of gastro-intestinal allergy revealed numerous types of symptoms and complaints as shown in Table 1. The indeterminate symptoms of dyspepsia, distention, belching, epigastric heaviness, pyrosis, nausea, vomiting, anorexia, upper abdominal uneasiness and soreness, and gastric upsets which so many physicians believe are due to gallbladder disease and which our experience has shown to be more likely due to the functional causes mentioned, are the most frequent complaints of those suffering from gastro-intestinal allergy. Because many such persons have organic disease

TABLE 1

ANALYSIS OF 100 CONSECUTIVE CASES OF GASTRO-INTESTINAL ALLERGY

<i>Types of complaints or symptoms</i>	<i>Frequency of Complaints</i>
Gaseous dyspepsia (belching, bloating, etc.)	38
Epigastric distress	22
Diarrhea	18
Vague symptoms referable to colon	17
Constipation	16
Nausea and vomiting	12
Abdominal uneasiness	11
Gastro-intestinal upsets	11
Cramps	10
Nausea	8
Nausea and vomiting	7
Epigastric heaviness	7
Distress in gallbladder area	7
Colic	6
Canker sores	4
Left upper abdominal pain	4
Pain in lower right quadrant	4
Abdominal soreness	4
Gastric upsets	3
Severe upper abdominal pain	3
Lassitude	3
Burning mouth	2
Blood and mucus in stools	2
Heavy breath	1
Anorexia	1
Ulcer symptoms	1
Family history positive for allergy	50
Positive personal history of other allergy	70

either in the gastro-intestinal tract or elsewhere, such as those having reflex gastro-intestinal symptoms due to primary abnormality in the urinary tract, it is obvious that organic disease must be excluded before allergy is considered as a possible cause, particularly if the complaints have not been present very long or if they have changed in character at some recent date. The type of examination indicated in these instances is mentioned elsewhere in this clinic.

Many patients complain of vague symptoms, and very frequently they have been present for years, often dating back to childhood and frequently the patient appears to have good

health in spite of his long history of abdominal discomfort. Patients with these complaints often give the examiner a clue by having a positive family or personal history of allergy or a history of very definite food disagreements or dislikes. As often as not, however, the patient is wrong about the foods causing his trouble, as shown by therapeutic tests under control conditions. Furthermore, cases are seen in which the symptoms come on during adult life, the patients fail to respond to the usual nonallergic management but do respond dramatically to treatment from the standpoint of allergy. Most of our cases of this type have been diagnosed by a process of exclusion and response to test diets; others have been suspected earlier because of manifestations of allergy in other parts of the body and skin tests have proved significant in these instances.

Case I.—A housewife, forty-five years of age, complained of almost constant distress in the abdomen. This had been present for two years and had been accompanied by intermittent distention, gas, bloating, and nausea. She believed the symptoms were made more severe by eating vegetables, lamb, and chicken.

There was no family history of allergy but the patient had had occasional attacks of urticaria and had been subject to migraine-like headaches for many years. Systemic review revealed no abnormalities and the physical findings were all within normal limits. A gastro-intestinal series' roentgen examination gave normal findings. The Ewald test meal gave a normal result. Intracutaneous tests for allergy revealed sensitivity to milk, wheat, orange, and tea. Elimination of these allergens has produced remarkable improvement in the gastro-intestinal and migraine-like symptoms over a period of one and one-half years.

Case II.—A housewife, thirty-eight years of age, complained of nausea and an "all gone feeling," which was present for days at a time and had occurred frequently for years. There was no family history of allergy. The patient experienced frequent colds and attacks of symptoms commonly ascribed to mild sinusitis.

Physical examination, laboratory studies, and roentgen examination of the gastro-intestinal tract revealed no abnormalities. The Ewald test meal showed a free acidity of 12 and a total acidity of 20.

Intracutaneous tests gave positive reactions to chocolate, milk, and tomato. Elimination of these foods resulted in disappearance of symptoms. There were no recurrences in two years.

Symptoms highly suggestive of a functional disturbance in the colon, such as cramplike or colicky pains, constipation,

flatulence, rumbling and gurgling, distress or pains in the lower abdomen, are complaints frequently mentioned by patients with allergy.

In our experience, many patients who have these symptoms of irritable colon, and, in addition, have signs and symptoms of other manifestations of allergy respond well to bowel management without any treatment of the allergy so far as their gastro-intestinal symptoms are concerned. Some patients have come under our care who have not experienced relief of their abdominal distress after excellent investigation and management of their allergy and have experienced prompt relief on bowel management. Often it is difficult to judge just what measures do produce relief because the physician is anxious to give the patient prompt relief and he may initiate principles of bowel management together with a regimen for the elimination of allergens. In these cases, unless there are other strong evidences of allergy, it is better to correct the functional, nervous, hygienic, and psychic factors before allergy is considered. Often such patients are harmed by unnecessary dieting because, with their attention focused on sensitivity to food, they will incriminate one food after another when, in reality, some other factor is responsible for their symptoms.

Case III.—A housewife, thirty-four years of age, had had chronic abdominal discomfort and burning of a generalized nature with intermittent gaseous distention and cramping abdominal pains for six years. One child had manifestations of allergy but the personal history was negative for allergy.

Physical examination, laboratory studies, and roentgen examination of the gastro-intestinal tract revealed no abnormalities.

Intracutaneous tests for allergy gave positive reactions to milk, rice, coffee, cabbage, chocolate, potato, tomato. Avoidance of these substances relieved the symptoms and there had been no recurrences eleven months later.

One must realize the importance of the psychological effect of studies for the determination of allergens on patients suffering with chronic dyspepsia. Many of these patients are absolutely certain that they cannot tolerate many foods, usually the so-called "acid foods" such as citrus fruits, tomato, and one or several kinds of meat and many have been treated by faddists or cultists by means of various and peculiar diets. If, instead of beginning their treatment by establishing normal habits and bowel function, one does skin tests and eliminates many more foods from an already restricted diet, there is

danger of increasing the food-phobia which will remain with the patient the rest of his life and seriously interfere with proper nutrition. We know that allergists have found that skin reactions are not significant in more than 50 to 65 per cent of cases but it is difficult to convince a neurotic or dyspeptic patient that a food to which he has a positive skin reaction is not poison to him; and it is even difficult to convince him that a negative reaction entitles him to eat a food he fears.

Recently, following the experience of Mackie,⁴ we have become interested in allergy as a factor in chronic nonspecific ulcerative colitis. We have patients in whom investigation and management of allergy have had a definitely beneficial effect. In most of our cases, improvement from allergy has been obtained when the ulcerative process had become more or less stabilized, having reached the stage of chronicity rather than being in the acute fulminating stage. The following case report is an example wherein the allergic management was a life-saving procedure.

Case IV.—A student, twenty years of age, complained that for six years he had had recurrent attacks of diarrhea for two to three weeks each spring and fall. During these periods, from two to six soft to fluid stools were passed daily, and associated with these attacks there was a daily elevation of temperature of 1° to 2° F. The patient had taken paregoric, bismuth, and a high vitamin diet without any change in symptoms. The patient's father and paternal aunts had asthma and the patient himself had seasonal hay fever.

At the time of examination the patient weighed 151 pounds, and his temperature was 99.2° F. No abnormalities were found on physical examination except for tenderness over the ascending colon. Examination of the blood and urine, the Wassermann and Kahn reactions, estimation of the blood sugar and Ewald test meal gave normal findings. Examination of the stools revealed nothing abnormal except for the presence of pus. Proctoscopic examination revealed normal findings.

Because of the presence of seasonal hay fever, investigation of allergy was started. Skin tests revealed a number of positive reactions including milk, wheat, orange, veal, corn, chicken, egg, carrot, and lettuce.

Roentgen examination, during and after the administration of a barium enema, showed a diminution of haustral markings and marked spasticity of the right colon as well as a narrowing of the terminal ileum. Roentgen examination after giving a barium meal confirmed these findings.

A diagnosis of regional ileitis and possible ulcerative colitis was made. The patient wished to return to school and to report at a later date for operation. Management for elimination of allergens was advised and six months later he returned, having been free from symptoms until two weeks prior to

the second admission when he again began to have diarrhea and fever. A recheck roentgen examination of the colon revealed no significant changes.

An exploratory laparotomy was performed. The last six or eight inches of the terminal ileum, the cecum, ascending colon, transverse, and descending colon to the proximal end of the sigmoid colon were markedly injected. There were many large glands in the mesocolon and mesenteric attachments of the cecum and terminal ileum. The operator was of the opinion that this was a case of ulcerative colitis. An ileostomy was made 16 inches proximal to the cecum. The glands removed for biopsy showed a well marked hyperplastic reaction with no evidence of tuberculosis or neoplasm.

The patient progressed very poorly following operation. He lost large quantities of fluids through the opening in the ileostomy, had marked fluctuations in blood chemistry, and lost 55 pounds in weight in spite of the use of intravenous fluid therapy, blood transfusions, high caloric diets, high vitamin diets, kaolin, belladonna, and other forms of management.

About five months later his life was despaired of and it was decided in consultation to place him on a trial diet of lamb, rice, and pears. Immediately following this he began to improve. He required no more intravenous fluids and the colostomy began to function normally. The weight at this time was 92 pounds. The patient gained approximately a pound a day until he weighed 132 pounds. As he improved, carefully selected foods were added to his diet.

Six months later when he returned, he was in excellent health, weighing 158 pounds. The ileostomy was functioning normally and roentgen examination of the colon revealed marked improvement in the findings. Two months later, a recheck roentgen examination of the colon showed entirely normal findings. Proctoscopic examination again revealed normal findings. At this time, it was decided to close the ileostomy. At the time of the operation, no evidence of abnormality was found in either the small or large intestine. No enlarged mesenteric lymph nodes were palpable. The ileostomy was closed and an entero-enterostomy and an appendectomy were performed.

The postoperative convalescence was entirely uneventful this time. Four days after operation, the patient was placed on the diet for the elimination of allergens which he had previously been following. When he was discharged from the hospital on the nineteenth postoperative day, the bowel function was entirely normal.

Diarrhea is not uncommonly a symptom of gastro-intestinal allergy. Usually it is part of an acute upset due to food allergy but in some patients diarrhea is chronic and is relieved by elimination of allergens and will recur if the patient ingests any of the offending allergens or a new sensitivity develops. Occasionally, patients will have diarrhea together with an attack of respiratory allergy such as hay fever or asthma.

Case V.—A man, forty-three years of age, had had since boyhood frequent attacks of abdominal discomfort and diarrhea for several days at a time. When

the diarrhea was most severe, the stools were bloody. He had frequent colds and his father was subject to hay fever.

Physical examination and examination of stools gave normal findings. Proctoscopic examination revealed normal mucosa for 10 inches. The Ewald test meal gave normal findings. Roentgen examination showed a very spastic colon.

Intracutaneous tests revealed positive reactions to egg, milk, corn, orange, and potato. Elimination of these substances produced marked improvement. No more severe attacks of diarrhea occurred during the next two years, although the stools occasionally were softer than normal.

Case VI.—A housewife, thirty-two years of age, complained of general lack of vitality. She had had extreme weakness five years before our examination and was relieved by intensive therapy with liver which was given orally for two months, but soon the weakness returned. For four years prior to admission, she had felt tired most of the time and any exertion seemed to cause extreme exhaustion in spite of adequate periods of rest.

The family history was negative for allergy and there was no personal history suggestive of allergy. Systemic review revealed no cause for the symptoms. Physical examination showed only poor nutrition and an asthenic habitus. She weighed 115 pounds, 9 pounds less than she did six months previously.

Laboratory studies gave normal findings except for a hypochromic anemia (4.2 million red blood cells, hemoglobin 52 per cent). The Ewald test meal gave normal findings.

With a diet for correction of the anemia and the administration of iron by mouth, she felt better when she returned two months later, and she had gained $1\frac{1}{2}$ pounds. The blood count was 4.9 million red cells and the hemoglobin was 75 per cent. Two months later she returned and said that she had had severe diarrhea, during the previous six weeks she had had two to ten liquid stools daily, and had lost 15 pounds in weight. The physical examination again gave negative findings except for redness and atrophy of the mucosa of the tongue. Stool, proctoscopic, and roentgen examinations of the colon gave normal findings. During several weeks' time the use of all the usual forms of nonallergic management were without avail in controlling the diarrhea.

In spite of the negative history of allergy, the patient was then placed on a diet of lamb, rice, and pears, as a therapeutic trial. Two days later the stools became normal, she began to gain weight at the rate of one-half pound a day, and felt so much stronger that she stated it was unbelievable. With gradual trial additions to her diet, the continued satisfactory progress has been truly remarkable.

Case VII.—A housewife, thirty-eight years of age, first had diarrhea three months prior to admission. Four to six fluid stools were passed daily. The stools contained a moderate amount of stringy mucus and were accompanied by sharp, cramping, abdominal pains which were relieved by defecation. Treatment had been a "course of calomel" at the onset and more recently bi-muth and paregoric had been used with little improvement. There had been a weight

loss of 8 pounds. The patient had had the seasonal type of hay fever for years and had mild asthma once. Her father had hay fever.

Systemic review gave normal findings. Physical examination showed only tenderness in the lower left quadrant and a spastic rope-like left colon. Examinations of the stools showed them to be normal. All examinations and tests gave normal findings; these included roentgen examination of the chest and gastro-intestinal tract, proctoscopic examination, Ewald test meal, blood counts and hemoglobin, Wassermann and Kahn tests, and sedimentation rate of the erythrocytes.

Since organic disease had been excluded, since there was a positive family history of allergy, and the patient herself had respiratory allergy, it seemed likely that allergy was the cause of the persistent diarrhea.

Intracutaneous tests revealed positive reactions to milk, egg, corn, rice, coffee, orange, pineapple, tomato, pepper, and asparagus. Elimination of these foods resulted in a prompt cessation of the diarrhea and relief of the cramping abdominal pains. There was no recurrence for several months, until she added milk in the diet. When milk was again eliminated her progress was satisfactory.

Nausea and vomiting, as symptoms of allergy, usually accompany some other manifestations of allergy, such as migraine, asthma, or acute abdominal crises due to allergy. The factor of allergy in cases of migraine headache and asthma is often apparent due to the presence of concomitant symptoms and signs and the response to ergotamine tartrate and adrenalin.

In the acute abdominal crises due to allergy, the diagnosis is often much more difficult. Occasionally, urticaria or angio-neurotic edema is present or a lead to the diagnosis may be gained by the finding of eosinophilia, a positive family or personal history of allergy, or the history of ingestion of some unusual food. The therapeutic trial of a dose of adrenalin is justified in all cases in which the physician suspects such a crisis. If the response is not satisfactory, it is probably best to proceed with surgical exploration unless the symptoms are out of proportion to the physical signs and it is deemed advisable to observe the patient for a longer period. At times, these acute abdominal crises are accompanied by gastro-intestinal bleeding. Most frequently, the physician will be called upon to make a differential diagnosis between an allergic crisis and acute appendicitis. In cases of doubt, it is better to operate and remove a normal appendix than to allow the appendix to rupture with the unfortunate sequelae that ensue.

Pain in the upper right quadrant of the abdomen or in the epigastrium which simulates gallbladder disease is sometimes a

manifestation of allergy. The diagnosis is often difficult, but with negative roentgen findings and with no response to ordinary measures for the relief of symptoms due to chronic cholecystitis, or to functional causes, it is worthwhile to consider allergy, particularly if there is absence of a history of definite biliary colic and if jaundice has not been present. The results of surgery are often very disappointing to both the patient and the physician in these borderline cases. Occasionally we have seen patients who have had operations for gallbladder disease and continued to have the same type of pain or distress after the operation, but who have made excellent response to management from the standpoint of gastrointestinal allergy.

Gastro-intestinal allergy is often manifested by pain in any one of the other abdominal quadrants and the pain may be sharp and acute and come in attacks or it may be chronic and irregular in occurrence. When it is chronic, it is most often due to common and frequently ingested food.

Case VIII.—A physician, thirty-six years of age, had suffered for six years with frequent attacks of severe midepigastic discomfort and belching. These occasionally were accompanied by attacks of vomiting, were not related to meals, and were not relieved by food, alkalis, antispasmodics, vomiting, or bowel movements. The patient believed that the ingestion of onions or shrimp provoked the attacks at times.

Repeated roentgen examinations of the gastro-intestinal tract revealed no abnormalities. Gastric analyses gave normal findings and duodenal drainage was negative. The patient had been advised to have an abdominal exploration.

There was no family or personal history of allergy. Systemic review gave negative findings and physical examination revealed no abnormalities. Laboratory studies gave normal findings.

Intracutaneous tests for allergy revealed positive reactions to milk, beets, mustard, tea, peaches, hops, pineapple. Elimination of these allergens gave complete relief of symptoms and the patient has been entirely free from attacks for three years except when he ingests milk.

Case IX.—A woman, forty-eight years of age, complained of frequent abdominal distress in the nature of bilious attacks with pain in the upper right quadrant for many years. At intervals for years she had had a burning sensation in her mouth. She believed coffee and oranges would induce the attacks.

There was no family history of allergy but the patient had allergic eczema at intervals. Physical examination and laboratory studies revealed no abnormalities. Intracutaneous tests showed sensitivity to milk, chocolate, potato, and cabbage. When last heard from fifteen months later she reported that elimination of these foods resulted in complete relief.

The relation of gastro-intestinal allergy to *peptic ulcer* should be considered when the patient with ulcer does not respond satisfactorily to the usual forms of management. The consideration of allergy in other ulcerative conditions in the digestive tract, such as ulcerative colitis, has been mentioned. Small mucosal erosions in the stomach and duodenum have been likened to "canker sores" in the mouth, and allergic management has proved effective in the relief of the latter condition. However, in our experience, the progress of the patient with ulcer, while using nonallergic management has been so satisfactory that allergy in these instances has rarely been considered. Patients with ulcer who had other manifestations of allergy and were found sensitive to milk by intracutaneous tests have made satisfactory progress while taking milk and cream at frequent intervals and following the other details of the Sippy regimen. At the same time, we have had rare instances of allergic individuals sensitive to milk in whom the response to management was not satisfactory until milk was eliminated from the diet.

Case X.—A white woman, twenty-eight years of age, complained of "digestive disorder." Since childhood she had been subject to frequent attacks of indigestion with nausea and vomiting. She had in recent years had epigastric distress irregularly during the day but was never awakened by it at night. She had not noted particularly the relation of food to the occurrence of the pain. For several years she had experienced frequent headaches, which sometimes were accompanied by nausea and vomiting and she believed that eating fried foods, fatty foods, and pastry caused the headaches.

The family history was negative for allergy.

Except for poor nutrition, the physical examination revealed no abnormalities. Laboratory studies, including an Ewald test meal, revealed normal findings. Roentgen examination showed a deformity of the duodenal bulb attributed to the presence of ulcer, but an active crater was not visualized. Although the presenting complaints were not characteristic of the well-known ulcer syndrome, the clinician thought that this might be an instance where the history was not reliable.

The patient was placed on a modified Sippy regimen.

She did not return until two and half years later, when she reported she had had only very slight relief from her epigastric distress on the Sippy regimen and that her headaches were more severe.

Allergy tests were made by the intracutaneous method. There were positive reactions to egg, milk, spinach, corn, onion, apple, chocolate, and tea. These foods were eliminated from her diet and in the ensuing three years she has experienced very marked relief from the headaches and the epigastric

distress, having a recurrence of symptoms only when she ingested milk, eggs, chocolate, or onions.

Edema of the lips or tongue may occur as the result of allergy and it is of varying severity. Usually the patient is able to determine the offending food without much difficulty. In some patients, there is merely itching, burning, or puckering of the mucosa due to a localized reaction. We recently saw a patient who had eaten no citrus fruits for years because of these local symptoms in the mouth. With the recent advances in vitamin therapy it is easy to correct such a vitamin deficiency with cevitamic acid.

We believe that at times canker sores are due to allergy to certain foods. When they occur infrequently a study to determine allergens is not indicated. When they occur in conjunction with some other condition due to allergy, elimination of allergens responsible for the major condition often decreases the frequency of canker sores. We have had under observation for over a year a middle-aged woman on whom complete studies for allergy were done because of frequent and severe canker sores. She has experienced great relief by following the regimen for elimination of allergens and this has been so complete that she cannot be induced to eat any of the foods to which she is sensitive.

Heavy breath and coated tongue at times are minor complaints of patients with allergy. These symptoms may be alleviated by proper management. In one of our patients whose chief complaint was heavy breath, relief followed the use of a diet free from allergens.

Itching about the anus or a sense of irritation in this region is occasionally relieved by treatment of allergy. Most often there are other manifestations of allergy, and it is seldom that pruritus ani as an isolated symptom is benefited by an allergic regimen.

SYMPTOMS OF GASTRO-INTESTINAL ALLERGY IN CHILDREN

Allergy is a frequent cause of gastro-intestinal symptoms in children. If one of the parents has allergy, this factor should be suspected and it should be even more strongly considered when both parents have allergy. Foods are the most important allergens in children and gastro-intestinal symptoms tend to accompany many other manifestations of allergy.

In hypersensitive children, the first contact with a food may cause violent symptoms, such as swelling of the oral tissues, vomiting, abdominal cramps, and diarrhea. In severe cases, the stools may be bloody. A family history of allergy, a history of ingestion of a food for the first time, other signs of allergy, such as asthma, eczema, or edema, and a blood eosinophilia are helpful points in differential diagnosis.

Colic in infants which fails to respond to ordinary measures of therapy, or colic in children of allergic parents should arouse suspicion of allergy. Often the response to some dietary changes is little short of spectacular. Persistent vomiting resembling pylorospasm or pyloric stenosis is at times due to food allergy.

Patients with cyclic vomiting⁵ have been treated on the basis of allergy with excellent results and this mode of attack on such problems holds much promise now.

Diarrhea is seen as a manifestation of allergy, usually as a part of an acute episode and not so often as the recurring intermittent type that is so commonly observed in adults. At times, though, diarrhea alternating with constipation is seen in children with allergy.

Anorexia and definite aversions to certain foods may be expressions in young children and infants of food allergy, and, if there are other factors that suggest allergy, investigation is necessary rather than insistence that the food be eaten.

DETECTION OF ALLERGIC FACTORS IN GASTRO-INTESTINAL DISTURBANCES

If the diagnosis of gastro-intestinal allergy is to be made in the proper proportion of cases, the physician's index of suspicion for factors of allergy must be raised. Every gastro-intestinal history should include a detailed family history concerning allergy and a detailed personal history concerning the occurrence of hay fever, asthma, frequent head colds, chronic sinusitis, migraine, eczema, hives, angioneurotic edema, food dislikes, foods that disagree, feeding difficulties as an infant or small child, cyclic vomiting, drug idiosyncrasies, and physical allergies. All these indicate to the physician that, if organic disease and obvious functional causes are eliminated, allergy may be a factor in producing the patient's symptoms.

Physical examination that reveals evidence of urticaria, angioneurotic edema, eczema, conjunctivitis of the allergic type, rhinitis with a pale, boggy nasal mucosa, asthma, or canker sores in the mouth again indicates that allergy must be considered.

The proper time for making complete investigation for allergy, after organic disease has been excluded, will of course depend upon many factors. In view of the time and effort needed for study of allergy, we believe a preliminary trial on nonallergic management should be instituted if the gastrointestinal symptoms predominate. If manifestations of allergy in other parts of the body predominate, investigation of the allergy is indicated at once. In these instances the gastrointestinal symptoms will be relieved with the disappearance of symptoms elsewhere in the body.

CHOICE OF TYPE OF ALLERGIC INVESTIGATION

The method used in finding the foods which are causing the patient's symptoms depends on several factors. One must consider the type of individual, how intelligent an observer he is, how frequently he will return to the physician for observation, whether other manifestations of allergy are present, the patient's state of nutrition, the severity of symptoms, and the patient's environment.

Obviously, one should not use the trial diets alone in a poor observer, an unintelligent patient, or one who will not cooperate well. Likewise, the travelling salesman or the student who eats at a boarding house or in a dormitory will find it difficult to cooperate in a method which requires special preparation of foods and frequent manipulations of the dietary regimen.

The patient who has other manifestations of allergy, such as hay fever or asthma and in whom inhalants may also be an important factor, should have skin testing, either by the scratch or intradermal method, as the initial step in diagnosis, being careful to explain to the patient that the method has been only 50 to 65 per cent reliable in a large group of cases, as far as food allergy is concerned, but that it may solve his difficulty immediately or again it may be necessary to use additional procedures until a solution of his problem is reached.

In patients who show skin reactions to most of the foods that make up their ordinary diet and in whom it will be a hardship to give up the articles of diet, it is well to check the results of skin tests either by the leukopenic index response or by dietary trial before final judgment is made as to whether the food is an offender.

In those persons in whom there is no familial history or other personal history of allergy and who have failed to respond to nonallergic management and who can be counted on to observe carefully and cooperate well and in whom it will not work a hardship to have meals prepared that are entirely different from the ordinary diet, we commonly begin with the trial diets which are similar to those advocated by Rowe⁶ and Alvarez.⁷

IDENTIFICATION OF FOODS CAUSING ABDOMINAL DISTRESS

Individuality in the prescription of diets is often necessary because of idiosyncrasies to particular foods. If your attacks of indigestion come at intervals of weeks, keeping a diary of foods eaten during the twenty-four hours preceding each upset should make the discovery of the offending foods comparatively simple. However, if your indigestion is present every day, considerable detective work may be required to identify the offending foods. Fasting or limiting the diet to maple sugar for a few days would probably result in complete relief of symptoms, but this is not pleasant and is usually impracticable. The following *Initial Diet*, which consists of foods least likely to cause distress, may be used for a period of four to seven days:

Soup: Lamb or mutton broth, containing rice if desired.

Meat: Lamb or mutton; roasted or served in the form of stew or chops; lamb patties or hash; cold sliced lamb; casserole of lamb and rice; lamb and rice croquettes.

Cereal: Rice krispies, puffed rice, rice flakes, rice flour, boiled rice, Pear juice or butter may be added.

Fruit: Pears, preferably baked with granulated sugar, pear juice, canned pears, stewed pears, or fresh pears without skin or seeds.

Sugar: Granulated or powdered only.

Fat: Butter or lamb fat only.

Seasoning: Salt only.

Beverage: Clear tea or water.

Suggestions.—For breakfast you may eat a lamb chop with puffed rice, rice flakes or steamed rice with butter or sugar, or some of the syrup from a can of pears. Cooked rice may be made into little cakes and fried in butter. For the noon and night meals you may have a lamb chop or roast lamb, again with rice and canned pears. No coffee, sodas, fountain drinks or candy should be taken, and even chewing gum should be avoided.

If your indigestion is not relieved, and fasting or limiting the diet to maple sugar is not feasible, limit the diet to milk only, taken as often as desired, for a few days.

If your indigestion has been relieved, add new foods, one each fourth to seventh day, in the following order: beef, potato, gelatin, carrots, turnips, asparagus, string beans, arrowroot cookies, rye crisp, thin toast, and oatmeal.

If constipation occurs, granulated agar, 1 to 2 tablespoonfuls at bedtime, may be taken, or plain water enemas may be used.

Your daily notes should include factors which commonly aggravate indigestion, such as eating when angry or in a hurry, emotional upsets, headaches, unusual fatigue, a "cold" or influenzal-like infections.

The above test diets are for diagnostic purposes only. They are not adequate or balanced diets and *should not be followed indefinitely*.

While the patient is following this trial diet, no medication is given except a drachm of dicalcium phosphate each morning before breakfast. The patient is impressed with the fact that he must take nothing else in the way of food or medicine. We also insist that he keep an accurate record of the symptoms he experiences while following this trial diet. If the response is not satisfactory, we shift to some other trial diet. If, however, the patient obtains relief from symptoms, we at once begin to add other foods, making additions about every four days. If some food is encountered which causes distress, we instruct the patient to omit the food until he is free from symptoms, then to try it and see if symptoms are produced again. This procedure is used until both we and the patient are convinced that the particular food in question is or is not an offender.

Because it is our desire to get the patient back on a balanced and adequate diet and a diet as nearly like that of members of his household as possible, wheat, milk, and eggs are tried as soon as possible after the patient has had a period of relief. Some clinicians prefer to try many other foods known to cause symptoms in only a few cases but we have found it more convenient to try these common articles of food early. When symptoms occur very infrequently, a food diary is often the means of finding the offender. Usually the food causing the symptoms has been ingested within the previous twenty-four hours before the onset of symptoms, but this is not always the case.

The use of Rowe's elimination diets is a helpful diag-

nostic procedure and there are other approaches, such as an initial period of starvation before any foods are given, which have their place in the attack on gastro-intestinal allergy problems but, in the main, we have found the use of the trial diet and skin testing with checks on important foods by the leukopenic index to be adequate and satisfactory.

Gastro-intestinal allergy in infants and children must be studied with care and discretion. Care must be taken to insure an adequate supply of minerals, vitamins, and calories even during the period of diagnosis. In infants and young children, a change to goat's milk or a formula prepared from soy bean flour often alleviates the symptoms and then a trial with superheated milk can be made. In young children, trial diets can be tried although they cannot be used for so long or be so restricted as in adults. Most satisfactory in studying sensitivities in children under ten or twelve years of age is to study tests done by the passive transfer method of skin testing.

TREATMENT OF GASTRO-INTESTINAL ALLERGY

Simply stated, the treatment of patients with gastro-intestinal allergy resolves itself into the elimination of foods which cause symptoms but the problem of treatment is more complex than this. The patient must be made aware of the occurrence of the offending substance, shown that it occurs frequently in prepared commercial foods, that it is an ingredient in many combinations that he had not considered before, and that he must be on the alert to detect such occurrences.

Further, to be adequate, treatment must include instructions to the patient for the preparation of adequate and palatable substitutes. Detailed directions concerning the planning of menus and recipes for appetizing and palatable dishes are imperative.

When milk, citrus fruits, wheat, or other foods containing important minerals or vitamins are deleted from the diet, adequate replacement therapy must be given in the form of calcium, phosphorus, and vitamins. With the numerous synthetic and concentrated vitamin preparations now on the market, this is much less of a problem than it was several years ago. To see that the patient receives the proper amounts of proteins, fats and carbohydrates is not difficult if attention is given to

the availability of substitutes now procurable through pharmaceutical and dietetic supply manufacturers.

The patient should be informed that, after a period of relief while abstaining entirely from the offending foods, he may be able to tolerate small or ordinary amounts of the present allergens. After the completion of allergic investigation we ordinarily wait several months before investigating the possibility of an increased tolerance to the foods that caused symptoms.

Elimination of foods which cause symptoms should result in complete relief but experience teaches us that, to obtain the best results, we must also give attention to deficiency states, metabolic and endocrine derangements, hygienic habits, and psychic disturbances before the patient is symptom-free. The correction of these factors proceeds along the same lines as when it is met in the nonallergic patient.

SUMMARY

Gastro-intestinal allergy, in our experience, is not rare but it is not as common as many workers emphasize. The possibility of allergy must be kept in mind during the study of a patient with gastro-intestinal symptoms but it is, of course, important to exclude organic disease and the usual functional disturbances first. This is done by careful history, physical examination, roentgen examination and laboratory studies.

Gastro-intestinal allergy is most likely to occur in patients with a positive family history or a personal history of other allergy. It is also a factor to be considered in the management of chronic nonspecific ulcerative colitis.

The detection of the offending substances is made chiefly by trial or elimination diets, skin testing, or digestive leukocyte response. In our hands the trial diets have proved satisfactory in many cases, but circumstances often dictate that skin testing is the initial procedure of choice. The final diagnostic criterion is the response of the patient to therapy.

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ALLERGIC BRONCHITIS

H. SCOTT VAN ORDSTRAND AND A. CARLTON ERNSTENE

THE three most common allergic diseases of the respiratory tract are bronchial asthma, hay fever and perennial allergic rhinitis. Respiratory allergy may also manifest itself in a fourth, less well recognized way, namely as allergic bronchitis. This condition is relatively common, may be either perennial or seasonal in form, and usually responds well to proper management. There is often an associated allergic rhinitis, and approximately one third of the patients report occasional wheezing during the time the cough is present. A few individuals experience typical attacks of bronchial asthma, and a review of the clinical history of certain patients with bronchial asthma, emphysema of the lungs and bronchiectasis indicates that untreated allergic bronchitis may be a forerunner of these conditions.

The symptoms of allergic bronchitis usually originate during childhood or young adult years and at times they even appear at the age of but a few months. The most significant feature of the disease consists of a persistent, relatively unproductive cough, occasionally paroxysmal in character, which occurs in the absence of pulmonary disease or evidence of infection in the upper respiratory tract. The cases are divisible into three distinct groups according to the duration of the cough and the presence or absence of seasonal occurrence. In the first of these groups there is more or less frequent cough throughout the year and in many patients this has been present for several years. Although the cough may be worse at night or at some particular time during the day, the season of the year has no effect upon it. In the second group, which seems to be the largest numerically, the patient complains of unusual susceptibility to "colds." A persistent cough develops at frequent intervals without relation to the season of the year and usually lasts for at least two weeks or longer. In the third group, the

cough is strictly seasonal, occurring in the spring or late summer, and is directly attributable to the pollens.

Physical examination of the patient who has allergic bronchitis frequently reveals nothing of significance. The lungs are entirely clear on percussion, and auscultation may give completely normal findings. In about one third of all patients, however, a few fine or medium moist râles are heard over all lung fields, and, in addition, there may be a few musical râles. An occasional individual in whom symptoms have been present without interruption for several years presents the barrel-shaped chest and other physical signs of chronic emphysema of the lungs. In unusual instances also undue diminution of the breath sounds over the base of the lungs and the occurrence of numerous medium and coarse râles suggest bronchiectasis but the presence of this condition must be confirmed by roentgenologic study after the instillation of iodized oil.

Roentgenologic examination of the lungs in patients with uncomplicated allergic bronchitis reveals entirely normal findings in somewhat more than one half of all cases. Occasionally in patients with severe cough of recent onset there is a more or less generalized increased density of the lungs of variable degree suggestive of an acute exudative process. These findings usually clear rapidly with proper treatment of the allergic state. In the remaining patients the shadows of the lung hilus are increased and there may be increased peribronchial shadows extending toward the periphery and especially into the lung bases.

Hypochromic anemia of mild or moderate degree is a frequent finding in patients with allergic bronchitis. The leukocyte count usually is within the limits of normal, but differential counts on stained films reveal a slight eosinophilia in a large proportion of the cases. The average finding is 4 per cent but in one of our patients who presented no other manifestations of allergy or of other pathologic states, 34 per cent of the white blood cells were eosinophilic leukocytes. The erythrocyte sedimentation rate is often slightly increased above the normal but greatly increased rates are encountered only in the presence of some complicating factor.

The principal allergens in a series of 60 consecutive cases of allergic bronchitis are presented in Table 1. As in other

TABLE 1

PRINCIPAL ALLERGENS IN 60 CONSECUTIVE CASES OF ALLERGIC BRONCHITIS

Allergen.	Number of patients tested.	Number of positive reactions.	Percentage of positive reactions.
House dust.....	60	54	90
Animal hairs and dander.....	60	54	90
Yeasts and molds.....	34	30	89
Feathers.....	60	44	73
Animal furs.....	8	5	62
Pollens.....	39	24	61
Orris root.....	60	33	55
Tobacco.....	60	33	55
Cottonseed.....	60	19	32
Silk.....	60	16	27
Pyrethrum.....	60	15	25

allergic states, multiple hypersensitivity is the usual finding but in many instances an analysis of the clinical history and inquiry into the patient's environment enable one to attach major importance to one particular substance. The response to the elimination or avoidance of this substance can then be employed as a test of the correctness of one's conclusions. In our patients the most important allergens were house dust, feathers, animal hairs and dander, and yeasts and molds. Food substances played a relatively unimportant part, and the pollens were the responsible agent only in the seasonal cases.

The most common complications of allergic bronchitis are, as one might expect, allergic in nature (Table 2). It is worthy of note that 6 of our 60 patients either gave a history of bronchial asthma or were observed during an attack. In these individuals the asthmatic attacks occurred at infrequent intervals but cough, which was regarded as due to allergic bronchitis, persisted between the seizures. Approximately one third of the 60 patients reported occasional transient wheezing dur-

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TABLE 2

ASSOCIATED CONDITIONS IN 60 CONSECUTIVE CASES OF ALLERGIC BRONCHITIS

Condition.	Number of cases.	Percentage incidence.
Perennial allergic rhinitis.....	25	42
Hay fever.....	7	12
Asthma.....	6	10
Allergic eczema.....	5	9
Gastro-intestinal allergy.....	1	2
Bronchiectasis.....	3	5
Emphysema of the lungs.....	2	3

ing or after paroxysms of cough, but there was nothing to indicate that this was to be interpreted as due to bronchial asthma. Bronchiectasis and emphysema of the lungs are unusual sequelae and are observed only in individuals who belong to the older age groups and have experienced symptoms for many years.

A positive family history of allergic diseases is obtained in approximately one half of all patients with allergic bronchitis.

Every patient with allergic bronchitis should receive a thorough physical examination after a detailed clinical history has been recorded. Particular attention should be given to the accessory nasal sinuses and the state of the nasal mucous membranes as well as to the pulmonary findings. Following this, roentgenograms should be made of the chest, and if either the roentgen findings or the results of the physical examination suggest bronchiectasis, additional roentgen studies should be made after the instillation of iodized oil into the bronchial tree. A complete blood examination including a careful differential count should be made, and the erythrocyte sedimentation rate should be measured. The sputum also should be examined.

The treatment of allergic bronchitis consists of elimination of the important allergens from the patient's environment whenever this is possible. When this is carried out successfully, prompt and complete relief from the cough is obtained. In

cases due to house dust and to yeasts and molds, the usual measures of cleanliness about the patient's house and place of business may not prove helpful. In these instances, an attempt should be made to immunize the individual by subcutaneous injections of suitably prepared extracts in gradually increasing concentrations. Similar treatment is employed in seasonal cases due to the pollens. The results of treatment are less satisfactory in cases due to house dust than in those due to other allergens, but even in this group at least partial improvement may be expected in a majority of the cases. Therapeutic measures other than the allergy regimen are seldom necessary although the temporary administration of iodides by mouth may be helpful in allaying cough before the regimen has been established.

ALLERGY AS A FACTOR IN HEADACHE

C. L. HARTSOCK AND F. J. MCGURL

HEADACHES of all types, severity and frequency present some of the most difficult diagnostic and therapeutic problems of medicine. From the heterogeneous groups of cephalalgias that torture human beings, only a few can be grouped into distinct clinical syndromes. The term migraine has been applied to one such characteristic symptom-complex. This periodic type of headache, with its prodromal and associated symptoms, is so thoroughly familiar to everyone that no description of its clinical characteristics is necessary.

Although migraine was recognized as a distinct clinical entity centuries ago, its etiology remained obscure in spite of the work of innumerable writers and investigators. The most accepted theory was that these periodic attacks were due to explosions of nervous impulses accumulating in a susceptible and usually high-strung, emotional person having inherited tendencies to migraine, the explosions being set off at intervals by a variety of trigger mechanisms.

On the basis of this theory, the treatment of migraine was not entirely unsuccessful in those cases where the emotional accumulation of energy could be controlled and the trigger mechanism made less sensitive or eliminated. However, success obtained at the expense of such drastic curtailment of the patient's activities really defeated its purpose. Few patients could afford the required inactivity and those who could rest were not temperamentally fitted or contented to do so during the most active years of their lives when unfortunately the attacks of migraine were at their peak of frequency and severity.

The treatment of migraine became a very discouraging problem. Attempts to relieve these miserable patients led to

many useless operations for the removal of suspicious foci of infection, pelvic organs and gallbladders. Such operations, of course, proved futile and the resultant drain on the patient's vitality usually served to aggravate the attacks. Consultants and clinics saw these discouraged patients in the interim between their attacks and tried vainly to give them some satisfaction and relief. As a rule, however, even following such studies, the family physician was still called upon to give the patient comfort during an attack or, in most cases, the patient finally reached the point where he resigned himself to twenty-four or forty-eight hours of invalidism at periodic intervals.

As the conception of allergy broadened and the rôle of human hypersensitivity to foreign proteins came to be understood as a cause of human ills, the possible relation of allergy to migraine was envisaged by a few observers. It really was not difficult to see this relationship. The inherited tendency was definite. Edema and spasm of the smooth muscles, the chief characteristics of allergy, could readily explain the symptoms of migraine. Furthermore, many patients had observed their own attacks sufficiently that they were able to trace the origin to the ingestion of certain foods. This was certainly a new and promising angle from which to approach this discouraging disease. Meeting some skepticism, it required considerable enthusiasm on the part of its earliest exponents to gain general acceptance for this new theory. As usual with new theories, there was overenthusiasm on the part of some workers and this led to glowing reports of brilliant results secured by the *elimination of allergens*. Such results could not be duplicated by others and this led to further skepticism.

It is true that all migraine-like headaches cannot be relieved by the strictest management for the control of allergy and the question arises as to whether there are other causes for this type of headache. We believe it can be stated that at the present time it is the general opinion of most observers, and the results of our own observations in every way confirm this opinion, that human hypersensitiveness plays a major rôle in the production of the migraine syndrome and the elimination of allergens offers the most satisfactory solution of the problem.

Before proceeding further with the discussion of the direct

treatment of the patient with migraine, some of the interesting features of this disease will be considered.

Patients with migraine are almost universally of the highly emotional or intellectual type or both. When attacks are spaced far enough apart for recuperation to take place between attacks, it is found that they usually follow some exhausting activity. The more or less continuous episodes of migraine occur only in those patients who show evidence of complete exhaustion. These facts and many others, such as the cessation of attacks during pregnancy and after the menopause, appear to indicate that a nervous and glandular factor is present in this disease. Can these facts be correlated with the theory of allergy as the origin of the disease?

Such a correlation is simple, of course, if one assumes that the sensitivity of the individual varies with his emotions and physical state. Similar phenomena have been observed to a lesser extent in other forms of allergy. The amount or quantity of the allergen to which the patient is exposed is a still more important cause of the variation in reaction. This quantitative factor is the one most affected by the nervous and physical state of the patient. Since the allergens which cause migraine are usually food allergens, the portal of entry must be the gastro-intestinal tract. To produce a reaction in the shock organ, it is probably necessary that the whole protein molecule to which the shock organ is sensitive be absorbed. Certain disturbances of the gastro-intestinal tract would permit this more readily than others, and we believe the conditions necessary for this absorption of whole protein molecules are more apt to be present in the gastro-intestinal tract when the patient is fatigued or emotionally upset.

Patients very frequently say that they have an unusual sense of well-being the day preceding an attack. It has also been observed that the fluoroscopic examination of the stomach and upper intestinal tract just prior to the onset of an attack shows a marked stasis or even a reverse peristalsis in the duodenum. My interpretation of these two phenomena is that, with increasing nerve tension and fatigue, a hyperperistalsis occurs which accounts for the sense of well-being. The hyperperistalsis then shifts to a reverse peristalsis and the resulting stasis in the upper intestinal tract, especially in the

duodenum, make ideal conditions for the absorption of whole protein molecules. The migraine syndrome has also been observed to have a direct relation to mechanical duodenal stasis and relief has been obtained by its correction. Variation in the activity of the digestive ferments and also the function of the liver during varying physical and emotional states of the patient could be additional factors favoring the absorption of the protein molecule.

These statements are entirely theoretical, but they are mentioned in an effort to explain some of the factors which must be considered if migraine is to be explained on the basis of allergy. This theory does have a practical application, however—for proper protection against the allergens to which the patient is sensitive, there must be a concerted effort to improve body function as a whole and reliance must not be based simply on exclusion of the causative allergens from the patient's diet.

Two groups of patients present important problems to the allergist who deals with the problem of migraine: (1) the patients with typical attacks of migraine but who do not respond to the strictest management for the elimination of allergens and (2) the patients with headaches not typical of migraine who, in desperation, are referred to him for possible aid. This latter problem is daily growing greater. The problem of the atypical case will be dismissed from this discussion with the simple statement that we have seen a sufficient number of cures to warrant a simple study for allergy and a brief regimen of dietary control if the patient understands that it is only an experimental attempt to determine the cause of his trouble. The intensive regimens outlined for the true migraineur should only be continued for a brief period of trial.

The patient with typical attacks who is not relieved by the most careful management cannot be dismissed so lightly. Such cases naturally bring up the question as to whether there are other causes for the migraine seizures. It would seem quite possible that other conditions might duplicate this syndrome; therefore, causes other than allergy should still be sought in addition to the attempt to find and correct factors that affect the allergy. Since this paper deals exclusively with the headache due to allergy, no further discussion of this phase of the problem can be given except to say that these patients remain

in the status quo of all patients before the importance of allergy as a cause of headache was appreciated and we must continue to treat them with every means at our disposal.

This statement in itself implies that a certain number of patients with migraine fail to respond to treatment of their allergy, and unfortunately this percentage is not small. Our experience, which coincides rather closely with that of other writers on this subject, shows that 25 per cent of patients suffering with typical migraine are not benefited in the slightest by the most strict regimens and direct efforts to eliminate allergy. A closer analysis of these cases reveals that most of these patients are extremely emotional. They were in a state of complete nervous exhaustion when the treatment was attempted. Even though they were more or less chronic invalids in a nervous way, aside from the attacks of migraine, it is difficult to reconcile the failure to relieve their headaches if all migraine is due to allergy. The best explanation is that the sympathetic nervous system has become so unstable that the mechanism producing the headache functions from other causes or continues to function even though all the stimuli from allergens have been removed. If these patients could have a long period of rest before the treatment for allergy is begun, the results might be more satisfactory. This is difficult because the attacks are so frequent that there is insufficient time between them for the patient to recuperate what was lost during the previous attack. This produces a vicious cycle that is difficult to break. Many such patients have found relief by using ergotamine tartrate but my experience with this drug is that the headaches are only allayed and the attacks come at more frequent intervals, so that little is gained in trying to restore the patient's general vitality.

On the other hand, 30 per cent of patients secure complete relief so long as they avoid the allergens to which they are sensitive and in this group have been included only those patients who find the routine easy enough that they cooperate completely in following instructions. The remaining 45 per cent include a heterogeneous group of patients who secure partial relief, *i. e.*, a decrease in the frequency or severity of the attacks or both. Some of these patients could easily be included in the group who secure complete relief if they would

cooperate fully. Others, in spite of good cooperation, experience only partial relief, while still others are only partially relieved because the routine is too difficult to be practical in their mode of living.

It can be stated that elimination of allergens favorably affects 75 per cent of all cases of migraine. The failure to secure results is directly proportional to the emotional stability that is present and the complete success, from the standpoint of practical application, is proportional to the ease with which the prescribed regimen may be carried out. The fewer and more defined the allergens which must be avoided, the more simple the routine for the patient and the more brilliant the results.

Determination of the causative allergens is of course the prime requisite for relief in any case. In simple cases, the patient will often have some ideas in regard to certain foods which should be restricted even though tests do not show reactions to these foods. We rely mainly on the intradermal skin tests for clues to sensitivity and base our original therapeutic regimen on the results of these tests, omitting also any food of which the patient is suspicious. If the diet, based on the results of the tests of sensitivity, fails to give complete relief, we then reduce the diet to the various well-known elimination diets. Failure after trial on several of these diets is quite discouraging in both patient and physician and temporarily, at least, we discourage further measures until the patient's general vitality has been improved. If this can be accomplished, another attempt at restriction of allergens is made.

Needless to say, the patient must be instructed to avoid allergens other than food allergens to which he is sensitive. A small percentage of migraine has been shown conclusively to be due to inhalant allergens.

The relation of allergy to migraine headaches is no longer in doubt. It offers more than any or rather all other types of management. There are, of course, difficulties and limitations, chief of which are the patient's inability or unwillingness to cooperate. The ability of the allergist to secure cooperation is no small part of the success. Fortunately, however, it is frequently no longer necessary to give a sales talk to convince

patients with migraine of the merits of giving allergic management a trial because more and more these patients come with the fixed purpose of being treated in this manner. This, in itself, speaks more than anything else for the success of this treatment because an inherent part of the personalities of these patients seems to be a desire to discuss their ills with their fellowmen. Now they are able to attend social functions which previously they often had to forego at the last minute because of a headache, and the relief of migraine has come to be as absorbing a topic of conversation as operations formerly were.

ATOPIC DERMATITIS

E. W. NETHERTON

THE application of knowledge concerning immunity and hypersensitiveness to the investigation of certain diseases of the skin has contributed much toward the solution of some of the common and complex problems of dermatology. This is especially true of eczema which, for many years, has been a subject of much debate among dermatologists. In the past, the term eczema has been used to designate a dermatosis which was thought to be capable of assuming many and varied clinical forms; consequently a large number of pruritic, erythematous, scaly, weeping, vesicular, papular, and lichenified eruptions were classified as various types of eczema. The lack of knowledge concerning the fundamental nature of these dissimilar eruptions was the principal barrier to a more comprehensive understanding of this difficult problem. To the critical observer, it seemed improbable that such a heterogeneous group of cutaneous lesions could all be manifestations of one particular dermatosis. Studies of the morphologic characteristics of the cutaneous lesions and the histopathologic changes which accompanied them led to important contributions but failed to produce specific information regarding the etiology or the mechanism responsible for the production of the eruption. It soon becomes apparent that the approach which offered the greatest possibility of progress was a more thorough study of the patient as a whole. The early, broad concept of eczema has become restricted as new dermatoses have been identified and removed from this large group of eczemas; however, many cases still remain in the eczema group in which the clinical course and the morphologic characteristics of the eruption vary widely. This variation is due to inherent qualities of the patients which are now known to influence their response to contact with irritants and antigens.

Individuals who have eczema differ from a normal person in their biologic reaction to environmental conditions and to activities which are essential to sustain life. They have either acquired or inherited a capacity to become sensitive to various substances. This constitutional predisposition is not possessed by normal individuals. It is now recognized that the dissimilar eruptions which are commonly called eczema are in reality the cutaneous manifestations of different types of hypersensitivity. Therefore, eczema belongs to the group of allergic dermatoses.

There are four types of cutaneous allergy: (1) contact dermatitis; (2) atopic dermatitis; (3) dermatoses due to bacterial and mycotic allergy; and (4) certain eruptions caused by drugs. Of these contact dermatitis and atopic dermatitis comprise the groups of cases which the average physician calls eczema; however, the dermatologist prefers to limit the meaning of the term eczema and consider it as synonymous with contact dermatitis.

Contact and atopic dermatitis differ in their clinical manifestations and in their mechanism of production; consequently for the sake of clarity and accuracy, it is desirable that eczema be dropped from the nomenclature of dermatology. This has been advocated by Sulzberger¹ and his coworkers, but it is doubtful whether a term so firmly established through usage by both the medical profession and the laity can be discarded so easily. If the term eczema is to be retained, its usage should be limited so as to designate contact dermatitis in which gross and microscopic vesiculation and exudation are present. For decades, these pathologic changes have been considered to be prominent characteristics of eczema. Contact dermatitis differs from atopic dermatitis in that it may be present at any age, but is very rarely seen in very young infants; it is not influenced by heredity; it is not frequently associated with other manifestations of allergy and it has a much better prognosis. In atopic dermatitis, the excitants or atopens stimulate an antigen antibody reaction but, so far, such a reaction has not been demonstrated in contact dermatitis. The shock tissue in contact dermatitis is the epidermis, while that in atopic dermatitis is located in the corium. A point of difference between contact dermatitis and atopic dermatitis which is of some

practical importance is that the incidence of each condition varies with each age group. Contact dermatitis which is the result of an epidermal hypersensitivity practically never occurs in the newborn infant but becomes more common during each decade up to approximately the fourth or fifth decade of life, while atopic dermatitis which is an immunological type of allergy usually makes its initial appearance as infantile eczema and decreases in incidence with each decade of life. It is seldom observed or makes its initial appearance in adults past thirty-five years of age.

Since, by far, the majority of the patients with cutaneous manifestations of allergy belong to the so-called "eczema" group, the space which is allotted to cutaneous allergy in this symposium is confined to the discussion of contact and atopic dermatitis.

Atopic dermatitis is a very complex type of cutaneous allergy and is one of the most difficult dermatoses to treat. Some individuals with atopic dermatitis are nervous, irritable, emotionally unstable, suffer from functional gastro-intestinal symptoms, present evidence of vasomotor instability, and experience an exacerbation of their eruption following fatigue or undue nervous strain. Because of this, some observers have felt that neurogenic factors play an important rôle in the causation and have applied the term *neurodermatitis disseminatus* (Brocq) to this syndrome. Other names have been suggested for this symptom complex but they are not mentioned for to do so would only tend to confuse the subject. Suffice it to say that atopic dermatitis or *neurodermatitis disseminatus* are the terms commonly used in the American medical literature.

Becker² has emphasized the etiologic importance of nervous instability in atopic dermatitis; however, Sulzberger, Spain, Sommin, and Shahon have aptly suggested that the hypersensitiveness and the emotionalism of nervous instability may be manifestations of the same underlying disturbance, although there is much to be said in favor of Becker's contentions. It is impossible to accurately evaluate the etiologic importance of these functional disturbances; therefore, it is best for the time being to consider this dermatosis as the cutaneous manifestation of atopy.

Coca³ was the first to use this term and has defined it in the

following manner: "By atopy is meant certain clinical forms of human hypersensitiveness that do not occur so far as is known in the lower animals and which are subject to hereditary influence." Asthma, hay fever, and atopic dermatitis, are the common manifestations of atopy. The frequent association of these three conditions has led to the recognition of a symptom-complex frequently referred to as the eczema-hay fever-asthma syndrome. It is not uncommon for an atopic individual to have one or more manifestations of atopy at the same time or for the clinical form of hypersensitiveness in the same individual to change from time to time. For example, hay fever or asthma may be associated with atopic dermatitis or in rare cases atopic dermatitis may disappear only to be replaced by asthma and after a period of time the asthma will clear up and the dermatitis return.

The influence of heredity in atopy is forcibly revealed in the family history of patients with this syndrome. The atopic individual usually has a unilateral or bilateral antecedent history of asthma, hay fever or atopic dermatitis, but in some cases a positive history of atopy in the immediate family cannot be obtained. Coca³ states that the incidence of hay fever, asthma, and possibly atopic dermatitis is highest in persons with a bilateral family history of atopy and also that the symptoms appear earlier than in individuals with a unilateral or negative antecedent history. Heredity further influences the clinical form of this type of hypersensitiveness in that it determines which shock organ is to be involved and to what group of atopens the individual will become sensitive.

Therefore, atopic individuals differ from normal persons in that they have inherited a constitutional predisposition to the development of hypersensitiveness to foreign proteins. The mechanism of atopy is complex. The future atopic patient is born without clinical manifestations of atopy but possesses a capacity to react in an altered or abnormal way following repeated contact with foreign proteins. This becomes manifested clinically by the appearance of the symptoms of asthma, hay fever, or atopic dermatitis. The number and the groups of proteins to which an atopic person may become sensitive and the frequency and degree of contact with the excitant which is necessary for the development of symptoms of atopy

vary with each individual. These factors are entirely influenced by heredity. Atopic hypersensitiveness is an immunologic phenomenon which is closely allied to anaphylaxis. The atopic individual also differs from a normal or nonatopic person in his biologic reaction to certain foreign proteins in that the proteins or atopens stimulate the formation of antibodies or reagins. These reagins which can be demonstrated in the serum of atopic patients are capable of sensitizing the skin of a normal person. This passively sensitizing property of atopic serum forms the basis for the technic of the Prausnitz-Kustner method of testing atopic patients for protein hypersensitiveness. There are many phases of atopy of which little or nothing is known; however, the occurrence of this atopen reagin reaction is sufficient proof that eczema-hay fever-asthma syndrome is a phenomenon of allergy.

Atopic reagins resemble anaphylactic antibodies in that they are immune bodies which are formed by antigenic stimulation, but differ in that they are not accompanied by the formation of a precipitin; they do not possess complement fixation properties; they are not capable of sensitizing the unstriped muscle of the guinea pig; and they usually do not neutralize the atopen.

This reaginogenic function does not occur in normal persons and so far as is known does not play a rôle in the mechanism of contact dermatitis or drug eruptions. This function is entirely dependent upon a hereditary predisposition and cannot be passively transferred to a nonatopic individual.

CUTANEOUS MANIFESTATIONS OF ATOPY

Atopic dermatitis usually appears early in life and most frequently starts as infantile eczema. In some cases, however, it does not develop until the atopic individual has reached childhood or adolescence. It is unusual for the cutaneous manifestations of atopy to first appear as late as early adult life and practically never after a person has become thirty-five years of age.

The duration and severity of atopic dermatitis vary with each patient. Infantile eczema, which usually appears during the first three months of life, may persist throughout childhood and into adult life. By the end of the second year of life,

however, most of the patients outgrow or lose their hypersensitiveness to the foods which caused the infantile eczema and the dermatitis disappears entirely and in many instances does not return; but, in some of these cases new sensitivities develop and recurrences of atopic dermatitis continue from childhood to early adult life. It is not uncommon for a patient with atopic dermatitis to give a history of having had infantile eczema for a few months, and of being free from atopic symptoms until late childhood or early adolescence. In a small percentage of cases, the symptoms of cutaneous hypersensitivity do not return until early adult life.

The clinical manifestations of infantile eczema are different from those of atopic dermatitis of childhood and adult life; nevertheless, both conditions are fundamentally the same disease. In both the eruption is a cutaneous manifestation of atopy. Hill and Sulzberger¹ have stressed this concept in their discussion of the evolution of atopic dermatitis. These authors divide the evolution of atopic dermatitis into three stages: (1) infantile eczema of atopic type, (2) atopic dermatitis of childhood (two to twelve years, neurodermatitis), and (3) atopic dermatitis in adults. This concept is supported by the fact that atopic reagins are known to be present in each of these stages of the disease and also by the history obtained from most of the patients with atopic dermatitis. Likewise, the evolution of the eruption has been observed in the same patient at different age periods.

Not only does the clinical picture of atopic dermatitis vary with different age periods but the number of atopens to which the patient has become sensitive varies. As the atopic patients grow older, they are exposed to more foods and environmental atopens, and, as a result, they are inclined to develop hypersensitiveness to many atopens. Most patients in the second and practically all of them in the third stage of atopic dermatitis have developed a polysensitivity. Although the reagins of many atopens can be demonstrated in the serum, only a few of the specific excitants which give positive skin tests play a causative rôle in a given case.

Infantile eczema is frequently preceded by the accumulation of yellowish, oil, or seborrheic, loosely adherent scales on the vertex and anterior portion of the scalp. Usually within six

weeks to three months after birth, an eczematous eruption develops on the cheeks.

The cutaneous manifestations of atopy which occur in infancy are usually polymorphic in type. The eruption most frequently starts as a papulovesicular dermatitis which is intensely pruritic. The small exudative papules are frequently excoriated and capped with small hemorrhagic crusts. As the eruption spreads to involve the cheeks and forehead, edematous, erythematous, weeping, and crusted, fairly well demarcated plaques are formed. In some cases the exudative feature is not conspicuous; consequently, the plaques are erythematous, dry, and scaly. It is not uncommon for the eruption to spare the eyelids and a zone about the mouth, but these areas are nearly always involved in severe cases of atopic dermatitis in the second and third stages of the disease. In time, lesions appear in other areas of predilection, namely, the forearms, wrists, and lateral surfaces of the legs. The trunk is frequently involved and in severe cases the eruption may become generalized. Nocturnal itching is a troublesome symptom and, unless the infant is restrained, the skin will be excoriated and otherwise irritated by scratching during the night. Although infants with eczema are often restless during the day and are deprived of quiet restful sleep at night, they are usually well nourished and in many cases overweight.

Atopic dermatitis of childhood presents a clinical picture which is different from that seen in infancy. The eruption is dry and papular rather than vesicular or exudative. There is no primary vesiculation. The face, sides of the neck, upper portions of the trunk, the wrists, and the antecubital and popliteal spaces are areas of predilection; however, lesions may be scattered over other areas of the body. Pale dermographia is often produced when the skin is scratched. In some cases the eruption may consist of small, erythematous papules, many of which have been excoriated, scattered over the face, neck, arms, and legs. The most characteristic lesions are the fairly well demarcated, dry, slightly scaly, erythematous or hyperpigmented thickened plaques which have a predilection for the antecubital and popliteal fossae. Because of the frequent occurrence of lichenified areas in these fossae, the term flexural eczema has been used to designate this condition. If the

eruption has been present for several weeks, the skin becomes hyperpigmented and the lesions are not so erythematous. Itching is intense and the more or less constant scratching or rubbing of the skin is the chief factor in the production of the lichenification. As previously stated, vesicles which are usually present in contact dermatitis do not occur in an uncomplicated case of atopic dermatitis in the second or third stage of the disease. However, the clinical picture may be complicated by a superimposed contact dermatitis due to an acquired hypersensitiveness to topical remedies or to other common external irritants.

Occasionally, atopic dermatitis may be complicated by vesiculopustular and crusted lesions of an impetiginous type. This is the result of a secondary pyogenic infection induced by scratching.

Disseminated neurodermatitis of the young adult, as previously stated, is usually observed in the small percentage of patients in whom the atopic dermatitis of childhood has continued to exist either more or less continuously or with periods of exacerbation and remission. A few patients who had infantile eczema may have been free from atopic symptoms during childhood or atopic dermatitis may have developed for the first time at this period in life. In many patients, the exacerbations are worse in the fall and winter. The skin on most of the areas of the body is dry, thickened, and hyperpigmented. These changes are particularly marked on the face, neck, and upper portions of the back and chest. The skin of the extremities is dry, hyperpigmented, and thickened, and in some cases almost ichthyotic. This is particularly marked in the antecubital fossae and on the flexural surfaces of the forearms. The skin on the trunk may be comparatively free from lesions or it may present to a lesser degree the changes seen on the face, neck, and extremities. Small, dry, excoriated papules may be scattered over the body, especially at points of pressure such as the waist line and on the buttocks. In long-standing cases, the eyebrows become thin and broken off, and the hair of the scalp may be dry and brittle. Small, crusted excoriations and areas of oozing may occur but are most numerous on the face, neck, and arms. This is probably due to the fact that the patient relieves the pruritus of the protected portions by rub-

bing the skin with the clothing while on the uncovered areas he resorts to scratching. Patients with atopic dermatitis seldom have acne vulgaris during their adolescence.

Stokes⁴ has stressed the importance of observing the personality of the atopic or diathetic individual. He has observed that these patients are alert, precise, and quick in action and have a masked or sphinxlike facial expression which is due in part to a controlled neuromuscular tension.

In rare cases, atopic dermatitis may be complicated by the development of juvenile cataract. It occurs in young adults who have had cutaneous manifestations for some time. Brunsting⁵ has recently reported 10 cases of disseminated neurodermatitis in which this complication occurred. In none of his cases was there any evidence of a congenital disturbance and he was also able to eliminate avitaminosis, endocrine dysfunction, or the ingestion of drugs as factors which might have contributed to the formation of the cataracts.

The patient with atopic dermatitis is usually free from any disturbance in general health. As Brunsting⁵ and others have stated, these patients are usually well developed but thin and rarely obese. Endocrine dysfunction is usually absent, although a mild degree of hypometabolism is not an uncommon occurrence and occasionally definite evidence of hypothyroidism is present. A differential blood count usually shows an eosinophilia which averages about 10 per cent.

It is well known that evidence of a neurocirculatory instability is frequently observed in patients with atopic dermatitis. It is impossible at the present time to estimate the importance of this imbalance of the autonomic nervous system as a causative factor in disseminated neurodermatitis. Many patients with this syndrome do not present signs of neurocirculatory instability which can be detected clinically. In addition, many patients with symptoms due to an imbalance of the autonomic system never have disseminated neurodermatitis or any other symptom of atopy, but may instead have lichen planus or circumscribed neurodermatitis, two conditions which differ fundamentally from atopic dermatitis, in that there are no circulating reagins and there is no evidence of a constitutional background of specific hypersensitivity. Therefore, in view of the present concept of atopy, it would seem more logical

to accept the suggestion of Brunsting⁵ and Sulzberger and his coworkers¹ that the vasomotor instability is probably subordinate to or a manifestation caused by the same underlying disturbance which is responsible for specific hypersensitivity. It is this fundamental, inherited, predisposition which makes the development of atopic dermatitis possible; however, the immediate exciting agents or atopens vary at different age periods. In their studies of the evolution of atopic dermatitis, Hill and Sulzberger¹ observed that the atopens to which the patients gave a positive test varied with each age period. They observed that the atopic patient is constantly developing new sensitivities and losing some of those he had earlier in life. They did skin tests on atopic patients at various ages and made the following important observations:

"That 85 per cent of all infants under one year of age that react to anything react to egg white, that the incidence of sensitivity to wheat nearly doubles between the sixth to the twelfth month and that few infants react to environmental exogenous atopens (inhalants) during the first year but that of these silk is the most important." The high incidence of positive reaction to egg white in infants who have not eaten eggs is striking. This is probably due to the fact that egg albumin, which is eaten by every pregnant woman, is readily absorbed undigested from the digestive tract and passes through the placenta into the circulation of the fetus. If the fetus has inherited a predisposition to sensitization, the atopen or egg albumin will stimulate the production of reagins which are responsible for the positive skin tests obtained before the infant has ingested egg protein.

In testing a group of patients with atopic dermatitis of childhood, Hill and Sulzberger¹ found that the incidence of positive reactions to egg and wheat decreased and, by the second year, sensitivity to milk tended to die out. However, the frequency of sensitization to inhalants (cat hair and silk) increased materially. In the adult group, they studied twenty-one patients with scratch or intracutaneous tests and observed that the incidence of positive reactions to other foods and inhalants increased. It is well known that only a few atopens will produce a positive test in adults with atopic dermatitis although it may be the cause of the dermatitis, and it is also known that

a negative test does not necessarily mean that a substance is not of etiologic importance. Nevertheless, these observations of Hill and Sulzberger¹ are important for they suggest a partial explanation for the continuation of the cutaneous manifestations in certain atopic individuals. This problem is very complex and no doubt there are other factors of which very little is known.

I have reviewed 50 selected cases of atopic dermatitis in adults and children which have been observed in this Clinic. Each patient had been investigated in the Department of Allergy by the same person; therefore, interpretation of the cutaneous tests is considered to be uniform. The average age of these patients was 19.5 years; there were 22 males and 28 females. There was a family history of allergy in 33 cases. There was a unilateral antecedent history of eczema in 15 cases while in only one case was there a maternal and paternal history of eczema. Thirty-seven patients gave a history of infantile eczema and 27 had associated allergies, usually hay fever or asthma. All the patients gave a positive reaction to many foods and in nearly every case there was a positive reaction to one or more of the inhalants. Twenty-four reacted to milk, 26 to egg protein, and 22 to wheat. All patients reacted to 4 or more foods, the highest number of positive reactions to food proteins in a single case being 53. The most significant finding in this small series of cases is that 48 patients gave a positive reaction to one or more of the inhalants. The environmental atopens which produced the highest incidence of positive tests were house dust, silk, orris root, and feathers. On several occasions, Sulzberger¹ has expressed an opinion that environmental atopens are important excitants of atopic dermatitis in adults.

It is not uncommon for an adult with atopic dermatitis, who has failed to improve following the elimination from the diet of the food which gives a positive reaction, to show marked improvement following a change in the environment. At the present time, I have under observation a girl thirteen years of age who has had atopic dermatitis more or less continuously since she was an infant. Studies for allergy revealed that she reacted positively to several foods and to house dust and orris root. She has failed to respond satisfactorily to an elimination

regimen but, when she spends her vacation in another part of the country, she is practically free from cutaneous manifestations even though she eats anything she desires. Within a few days after she returns home, the eruption recurs. Patch tests for epidermal hypersensitiveness have given negative reactions and the eruption is always of the dry, papular, lichenified type which involves the face, neck, and antecubital spaces. The improvement which is obtained by a change in environment is no doubt partially due to rest, relaxation, recreation, and exposure to sunshine, but it does not seem probable that these are the chief factors, especially since the symptoms return shortly after she returns to her habitual environment.

I have observed other patients with atopic dermatitis who have had a similar experience following a complete change in their environment. They have all been young adults or in their late childhood. Apparently, environmental influences are important in cases of this type and the opinion expressed by Sulzberger and others that inhalants are important excitants in atopic dermatitis needs further investigation.

DIAGNOSIS

In most cases of atopic dermatitis, the diagnosis is not difficult. A careful history is of prime importance. An antecedent history of asthma, hay fever, or eczema is very significant and, if the patient has a past history of infantile eczema, hay fever, or asthma, he is an atopic individual.

There is always an involvement of the face, neck, upper portion of the chest and the flexural spaces of the knees and elbows sometime during the disease; however, in the mild cases or during periods of partial remission, the antecubital fossae may be the only regions affected. In uncomplicated cases, the eruption is dry and papular or the skin is thickened or leathery. Itching is paroxysmal and is usually made worse by fatigue and emotional strain. Vesiculation which is characteristic of contact dermatitis and which is commonly seen in dermatoses due to mycotic allergy is practically always absent. Polysensitization to proteins as demonstrated by skin tests is always present while epidermal hypersensitivity as demonstrated by the patch test is usually absent. To avoid repetition, a more detailed discussion of the differential diagnosis is not

given. The diagnostic characteristics of the allergic dermatoses have been given by Dr. Curtis in his discussion on contact dermatitis.

THE MANAGEMENT OF ATOPIC DERMATITIS

The management of atopic dermatitis is an extraordinarily difficult task and the results which are obtained are, in most cases, very discouraging. The best results are obtained in infantile eczema and in young children. The treatment consists of: (1) attempts to prevent contact with the excitants which are known to be of etiologic importance, (2) procedures intended to desensitize the patient to offending atopens, (3) symptomatic or palliative measures intended to relieve itching and to decrease the nervous irritability which is so frequently present.

There is no satisfactory method of testing the patient who has atopic dermatitis which enables us to determine in a short time what particular protein or proteins are important etiologic factors. At present, the most commonly used procedure is to do skin tests either by the direct (intradermal injection) or by the Prausnitz-Kustner method (passive transfer). This type of investigation is unsatisfactory, for experience has shown that a positive test does not necessarily mean that the atopens which are responsible for positive reactions are factors in the causation of the symptoms. Some of the positive reactions are probably nonspecific. The difficulty in interpreting the results of these tests is increased in the adult patients who almost universally show a polysensitivity (Mendelsohn⁷). Because of this difficulty, many dermatologists feel that intradermal tests are of little value in demonstrating the cause of disease. Intradermal tests are of value, however, in that they show that reagins are present, thereby proving that the allergy is of the immunologic type. They also form a basis for the formulation of an elimination regimen. It is important that the real significance and the limitations of the results of these tests be explained to the patient or some responsible member of the family. Too often, the patients are of the opinion that a positive test means that the specific food is causing their symptoms and will voluntarily restrict their diet to the point of producing a deficiency, thereby impairing their health.

Use of the elimination diets, advocated by Rowe,⁶ is a valuable way of attempting to eliminate the food factors which may be important in atopic dermatitis. In fact, such diets must be used even though intracutaneous tests have been done and it is the only method which is available to estimate the etiologic importance of any particular food. Brunsting⁵ believes that a strict regimen of dietary control is unnecessary. He feels that for sensitive persons the most common food irritants are eggs, nuts, fish, and other sea foods, pork, tomatoes, fresh berries, chocolate, cheese and condiments, spices and coffee.

A regimen confined only to the elimination of food irritants is seldom followed by marked improvement. Occasionally, in young children who have not developed a multiple hypersensitivity, marked satisfactory results are obtained.

The elimination of the environmental atopens is even more difficult and in most cases impossible. Contact with silk is decreased by eliminating silk clothing, feathers should be removed from the bed or the pillows properly covered, pets should be prohibited and floor coverings removed and furniture thoroughly and frequently cleaned with a vacuum cleaner. It is obvious that patients who are sensitive to environmental atopens cannot spend their life in an air-conditioned atmosphere; however, these procedures will decrease if not entirely eliminate contact with the inhalants which are most important. In severe recalcitrant cases the patient should be advised to try a change in environment. A warm, dry, sunny climate should be chosen.

Attempts to desensitize patients to foods and inhalants have failed. Some allergists feel that injections of extracts of the inhalants are of value in some cases but in the cases I have observed the results of this type of therapy have been rather disappointing.

Symptomatic or palliative procedures comprise the most important part of the management of atopic dermatitis. There is a tendency in most cases for the disease to subside or decrease in severity as the patient grows older, and likewise partial or complete remissions are common; therefore, mild cases of atopic dermatitis will do well under symptomatic management.

Symptomatic treatment is divided into: (1) the application

of topical remedies to prevent or to decrease the pruritus and (2) measures intended to decrease the nervous and mental stress of the patient.

During the acute stage of an exacerbation, bland applications are the most valuable type of topical treatment. Continuous applications of packs consisting of three or four layers of gauze saturated with calamine liniment and 1 per cent phenol are often beneficial in the early, erythematous, oozing stages of an acute exacerbation. If the oozing is a marked symptom, moist packs of aqueous solution of aluminum acetate (one teaspoonful to a pint of warm water) may be used instead of the calamine liniment. As the acute reactions subside, the liniment should replace the moist packs. As the dermatitis becomes subacute a bland or slightly stimulating salve should be used. Oftentimes marked relief will be obtained following the use of an ointment of 5 to 10 per cent boric acid and 1 per cent phenol in white vaselin. Ichthyol, in 3 to 5 per cent strength, when incorporated in zinc oxide ointment, is also a valuable remedy in subacute cases. Naftalan in 5 to 10 per cent strength in zinc oxide is a valuable mild stimulating and antipruritic ointment. In the subacute cases it is best to proceed carefully with stimulating ointments, because if stimulating ointments are used too soon the dermatitis will become aggravated.

Tar is one of the most valuable of all antipruritic remedies and its use is especially indicated in patients with dry lichenification, such as occurs in disseminated neurodermatitis. Various preparations of tar may be used but it is best to become familiar with one or two types of tar and to use them to the exclusion of all others. The crude coal tar zinc oxide paste recommended by White⁸ for use in infantile eczema is one of the best preparations available. This is an especially valuable application for the moist oozing exacerbations.

The formula which we have used is crude coal tar, 8 Gm., zinc oxide, 8 Gm., starch and white petrolatum, each 60 Gm. At times this paste is too drying and it becomes necessary to eliminate the starch. A more pleasant preparation is liquor carbonas detergens, 10 to 15 per cent in a base of boric acid ointment or petrolatum and hydrous wool fat. Ung. picis liquide zinc oxide and starch paste is a most pleasant and potent

antipruritic salve. It consists of ung. picis liquide 4 Gm., zinc oxide, 4 Gm., pulverized starch, 8 Gm., ung. diachylon, 4 Gm., and white petrolatum, 30 Gm. The two zinc oxide and tar preparations just mentioned become adherent to the skin and must be removed at least every other day by rubbing a little olive oil or liquid petrolatum into them. The ointment can then be removed without any difficulty. The best way to apply the ointment is to spread it lightly over the involved areas and then to apply a layer of gauze held in place by a loosely applied bandage to the areas not covered by clothing.

Soap and water should not be used too freely. Daily starch and soda baths with the use of a bland soap every second or third day are usually beneficial and sufficient.

Roentgen ray therapy is very useful in atopic dermatitis. The itching usually subsides rapidly and the eruption shows marked improvement and will usually disappear following a series of eight to ten treatments or less, depending upon the severity of the case. Unfortunately, the benefit obtained from this procedure is only temporary and if used by the inexperienced there is grave danger of producing an x-ray dermatitis. This type of treatment should be reserved for chronic cases which have failed to respond to more conservative treatment or for the relief of symptoms in a severe exacerbation.

Ultraviolet radiation has been recommended for the treatment of atopic dermatitis, but it has been my experience that its value is very limited.

Brunsting⁵ feels that nonspecific foreign protein and auto-hemotherapy are sometimes beneficial. My experience with this type of therapy is limited; however, in the few cases in which it was tried, the results were poor.

The general condition of the patient should not be overlooked. Self-imposed dietary restrictions may result in deficiencies. Many patients will have a mild secondary anemia and in some cases there is an associated achlorhydria. Patients on a rigid elimination diet should be given vitamin concentrates, iron and calcium. Calcium is best administered in the form of dicalcium phosphate. If achlorhydria is present, dilute hydrochloric acid should be added to the medication.

Even though patients with atopic dermatitis usually have a basal metabolic rate within normal range, many will be bene-

fited by small doses of thyroid extract. This extract should be given in all cases in which there is a low basal metabolic rate.

One of the most important remedies for the treatment of disseminated neurodermatitis is rest. The rest should be as complete as possible and is best obtained by placing the patient in the hospital. Many obstinate cases will show marked improvement or clear up entirely following a stay in the hospital from two to four weeks. The patient is not only relieved of the emotional and nervous stress incident to the vexing problems which arise in every family from week to week, but is prevented from coming in contact with the environmental atopens of the home. The benefit which is derived from hospitalization is probably due to both the rest and the change in environment. Many times the benefit obtained from hospitalization is only temporary; consequently, it is inadvisable or impossible for many of the patients to assume the expenses necessary for hospital care.

The stress of social and business activities should be kept down to a minimum. The atopic school child should not be pushed with his school work. In the treatment of the ambulatory patient, nerve sedatives should be used, especially during the exacerbations of the disease, but should not be given continuously over a long period of time. A teaspoonful of the following mixture will usually suffice: tincture of belladonna, 14 cc.; sodium bromide, 20 Gm.; and elixir phenobarbital, q.s. ad 120 cc.; to be taken after each meal and on retiring. If insomnia is a troublesome symptom, a hypnotic should be given but only for a few nights. Patients who present signs of marked neurocirculatory imbalance should be seen by a neuropsychiatrist.

At best, the results of treatment of atopic dermatitis are very disappointing to both the physician and the patient. Very few, if any, adult patients who have had their disease more or less continuously since infancy or early childhood can be cured. Improvement may be obtained in some cases, but many continue to have exacerbations with partial remissions, regardless of what treatment is used. In some cases, there is a tendency for the severity of the cutaneous manifestations to subside as the patient grows older. The atopic patient has inherited a constitutional background which cannot be altered

by any present-day therapeutic procedures. Whether the cutaneous manifestations of atopy are due to protein hypersensitivities which the atopic person develops or whether the nervous instability, which is frequently observed in these patients, is of prime etiologic importance remains a debatable question. It is probable that the immunological phenomenon and the vasomotor instability are manifestations of the same underlying constitutional disturbance.

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BRONCHIAL ASTHMA: CAUSES AND TREATMENT

RICHARD S. KNOWLTON

ASTHMA is a term used to describe a recurrent and paroxysmal type of dyspnea which is characterized by a wheezing or whistling type of expiratory respiration. Bronchial asthma due to allergy is thought to be caused by obstruction of the smaller bronchioles by narrowing of their lumens from spasm of the bronchial muscles or by swelling of their lining of mucous membrane.

The constitutional predisposition of the patient is an important factor in a consideration of the etiology of bronchial asthma. Allergy shows a definite tendency toward hereditary transmission. Hypersensitiveness is probably a mendelian dominant as shown by Cooke and Vander Veer;¹ however, persons who have a familial history of allergy have a constitutional predisposition to asthma which may develop under proper environmental influences and with adequate contact with allergens.

The glands of internal secretion apparently are influential in precipitating allergy at certain times. The onset of puberty, menstruation, and the menopause may initiate an attack of asthma, and in many cases pregnancy effects a complete remission of symptoms. Nervous and psychic influences are undoubtedly etiologic factors in asthma, but probably do not initiate an asthmatic attack except in individuals with a predisposition for this condition.

The rôle of infection is of great importance in the etiology and course of bronchial asthma. An acute infection often causes the initial attack of asthma, and this is especially true of an infection in the upper respiratory tract, such as whooping cough, pneumonia, influenza, or a nonspecific bronchitis. The part played by chronic infections and tuberculosis is much less clear, although the removal of focal infection in the sinuses, teeth, or tonsils is often accompanied by considerable relief.

Mucous nasal polyps are undoubtedly secondary to nasal allergy and, although sinus disease may frequently be found in the patient with asthma, its existence does not necessarily mean that the sinus is a primary etiologic factor. The constant drainage of pus from infected paranasal tissues may produce direct irritation of the bronchi, especially when it passes into the trachea and lungs during sleep. Kelley² studied 100 patients with bronchial asthma and found that 89 per cent had a chronic hyperplastic sinusitis involving one or more sinuses. Sixty of the 89 patients with hyperplastic sinusitis presented allergic nasal membranes and 23 of these had nasal polypi.

Food allergy is a common cause of bronchial asthma, especially in children. In most cases, the elimination of food allergens is an important adjunct in the control of asthma caused primarily by inhalants or bacterial allergens. Asthma that begins during the first two years of life, especially when preceded by eczema or disturbances of the gastro-intestinal tract, suggests food allergy. When food asthma starts in childhood, it sometimes becomes chronic and persists with varying intensity into adult life. Asthma due to food allergy may arise, however, at any time during adult life.

It is well known that bronchial asthma may be due to inhalant allergens such as dust, pollens, animal danders, orris root, seeds, and miscellaneous inhalants. Pratt,³ by use of skin tests, determined that approximately 79 per cent of children who suffer from perennial asthma between the ages of one and twelve years are sensitive to extracts made from house dust. Seasonal hay fever and asthma due to molds⁴ are definite and important causative factors in bronchial asthma. The spores of the fungi are air-borne, are seasonal during the warm months, and sensitivity is manifest by positive reactions to the mold extract as determined by intracutaneous tests. The good results secured following desensitization with the mold extracts are often very dramatic.

Seasonal bronchial asthma due to the pollens and especially to the ragweed pollens prevalent in the fall is not an infrequent cause of bronchial asthma. These patients have asthma at no other time of the year and it is promptly relieved by desensitization to the pollens.

REVIEW OF 100 CASES

The following is a summary of the outstanding findings in 100 consecutive cases of bronchial asthma. In this group of cases of allergic bronchial asthma, the primary etiologic factors were specific antigens which were the result of inhalants, foods, or bacterial allergens, or a combination of all three.

INCIDENCE OF ALLERGY AND INFECTION

In this series, there were 77 cases of purely allergic bronchial asthma and 23 cases of allergic and infectious bronchial asthma. The infection in the 23 cases was characterized by purulent sputum and was secondary and superimposed on primary allergic bronchial asthma.

Sex.—There were 54 males and 46 females.

Age.—The following table shows the ages of these patients:

AGE	
<i>Number of Cases</i>	<i>Age in Years</i>
4	Less than 5
16	5 - 10 years
8	10 - 20 years
11	20 - 30 years
21	30 - 40 years
19	40 - 50 years
14	50 - 60 years
7	Over 60 years

Family History.—Forty-five patients had a definitely positive familial history of allergy.

Specific Allergens.—Complete tests for allergy were carried out in every case. The passive transfer method was used for the infants and the smaller children. The scratch and intracutaneous methods were used for all other tests. Only the most common offenders and the most common and universal inhalants and foods are cited in the following tabulations:

1. **Feather Inhalants.**—Seventy-two per cent of patients had positive reactions to chicken, duck, and goose feathers.

2. **Hair Inhalants.**—Thirty-one per cent of patients gave positive reactions to camel hair; 42 per cent to horse hair; 33 per cent to rabbit hair; 43 per cent to dog hair; 28 per cent to goat hair; 32 per cent to cat hair, and 30 per cent to cattle hair.

3. **Miscellaneous Inhalants.**—Eighty-seven per cent of patients gave positive reactions to house dust; 17 per cent to flaxseed; 56 per cent to orris root; 25 per cent to pyrethrum; 29 per cent to silk; 41 per cent to tobacco; 30 per

cent to cottonseed; 25 per cent to kapok seed; 38 per cent to yeast, and 41 per cent to the molds.

4. **Pollen Inhalants.**—Twenty per cent of patients gave positive reactions to tree pollen; 27 per cent to grass pollen, and 34 per cent to ragweed pollen.

5. **Foods.**—Twenty per cent of patients gave positive reactions to beef; 21 per cent to lamb; 22 per cent to pork; 45 per cent to egg; 73 per cent to milk; 33 per cent to corn; 38 per cent to oats; 36 per cent to rice; 16 per cent to rye; 69 per cent to wheat; 28 per cent to chocolate; 30 per cent to orange; 33 per cent to white potato, and 37 per cent to tomato.

Roentgen Examination of the Chest.—Roentgen examination of the chest was made in 71 instances. In 55 per cent of the cases, the findings were normal and in 45 per cent there was extensive fibrosis at the hila extending well out into the middle of the lung. None of the patients with normal chests had any evidence of bronchial infection. One patient had an associated silicosis, and one patient had a complicating bronchiectasis.

Sedimentation Rate.—By our method, the sedimentation rate is normal up to 0.35 mm. per minute. All the patients with bronchial infection had an elevated sedimentation rate. The readings varied from 0.45 to 1.25 mm. and averaged 0.9 mm. per minute. The sedimentation rates of the patients with uncomplicated allergy averaged 0.47 mm. per minute and ranged from 0.15 to 1.3 mm. per minute, 54 per cent of the readings being above normal.

Miscellaneous Findings.—Four patients had chronic pulmonary emphysema, three patients had essential hypertension, and four patients had positive skin tests to pollen, but no clinical symptoms of seasonal hay fever. These patients were benefited by pollen immunization.

ASSOCIATED ALLERGIC MANIFESTATIONS

The associated manifestations of allergy in these 100 cases were:

Perennial allergic rhinitis	59
Seasonal hay fever	34
Infantile allergic eczema	13
Hyperplastic sinusitis	15
Nasal polyps	14
Migraine	11
Hives	9
Gastro-intestinal symptoms of allergy	7

TREATMENT

The treatment of patients with bronchial asthma consists of the following measures:

1. Elimination of inhalant allergens from the environment. Pillows and mattress may be covered with an allergen-proof encasing; dust in the bedroom may be prevented by making it as barren as possible and by using washable rag rugs. Pets are not allowed in the house and nonallergic cosmetics are used.

2. The elimination of positive food allergens from the diet.

3. Desensitization therapy by subcutaneous injection of extracts of the inhalant allergens when the reaction to them is markedly positive and when contact cannot be avoided easily, as in cases of house dust, molds, orris root, or the animal danders, and when the pollens give a positive reaction.

4. Immunization with autogenous bacterial vaccine by subcutaneous injection if any degree of infection is present. Such vaccines may be prepared from nasal or bronchial secretions. When positive reactions to skin tests are secured, they have given encouraging results.

5. Rest. Moderate physical exertion and sudden changes in temperature often precipitate an attack of asthma which could be avoided by proper rest.

6. Adequate amounts of vitamins A, B, and D should be provided. This is especially important when the diet by necessity is deficient in these substances.

7. Control of any secondary anemia as a general measure.

8. The elimination of foci of infection.

9. Use of an asthma mixture consisting of:

Sodium iodide	℥iv
Fluidextract lobelia	℥xv
Fluidextract hyoscyamus	℥xv
Fluidextract grindelia	℥j
Glycerin	℥j
Elixir simplex	℥. s. ad ℥iv
Sig: One teaspoonful four times daily.	

Added iodides are often given by mouth or intravenously. This mixture effectively loosens the tenacious bronchial secretions.

10. Ephedrine and amytal capsules by mouth to relieve bronchial spasm.

11. Adrenalin as inhaled vapor or by subcutaneous injection as necessary for the relief of acute attacks.

12. Glucose in a 25 per cent solution is administered intravenously each day, 250 cc. being given twice or three times daily in severe cases when an acute attack may be precipitated by any oral intake of food.

13. The instillation of iodized oil into the trachea is of value to patients with considerable chronic or prolonged asthma which has not responded well to the usual methods of therapy. The iodized oil brings up bronchial secretions and it may have some antiseptic properties.

14. Attacks of intractable asthma are often alleviated by the use of rectal ether narcosis, the dosage for an adult being 2 to 4 ounces of anesthesia ether in 8 ounces of olive oil. This may be repeated every hour until the patient is relaxed.

15. Morphine is avoided because of its associated reactions. The most undesirable effects are excitation and emesis which, if present, often make the condition of the patient worse.

16. Adequate sedation.

SUMMARY

1. Bronchial asthma is a disease due to allergy and the allergens may be inhalants, foods, organisms, or physical agents.

2. The most important inhalant allergens are house dust, feathers, animal danders, orris root, tobacco, and the pollens.

3. The most important food allergens are milk, wheat, egg, oats, chocolate, tomato, fish, coffee, and orange.

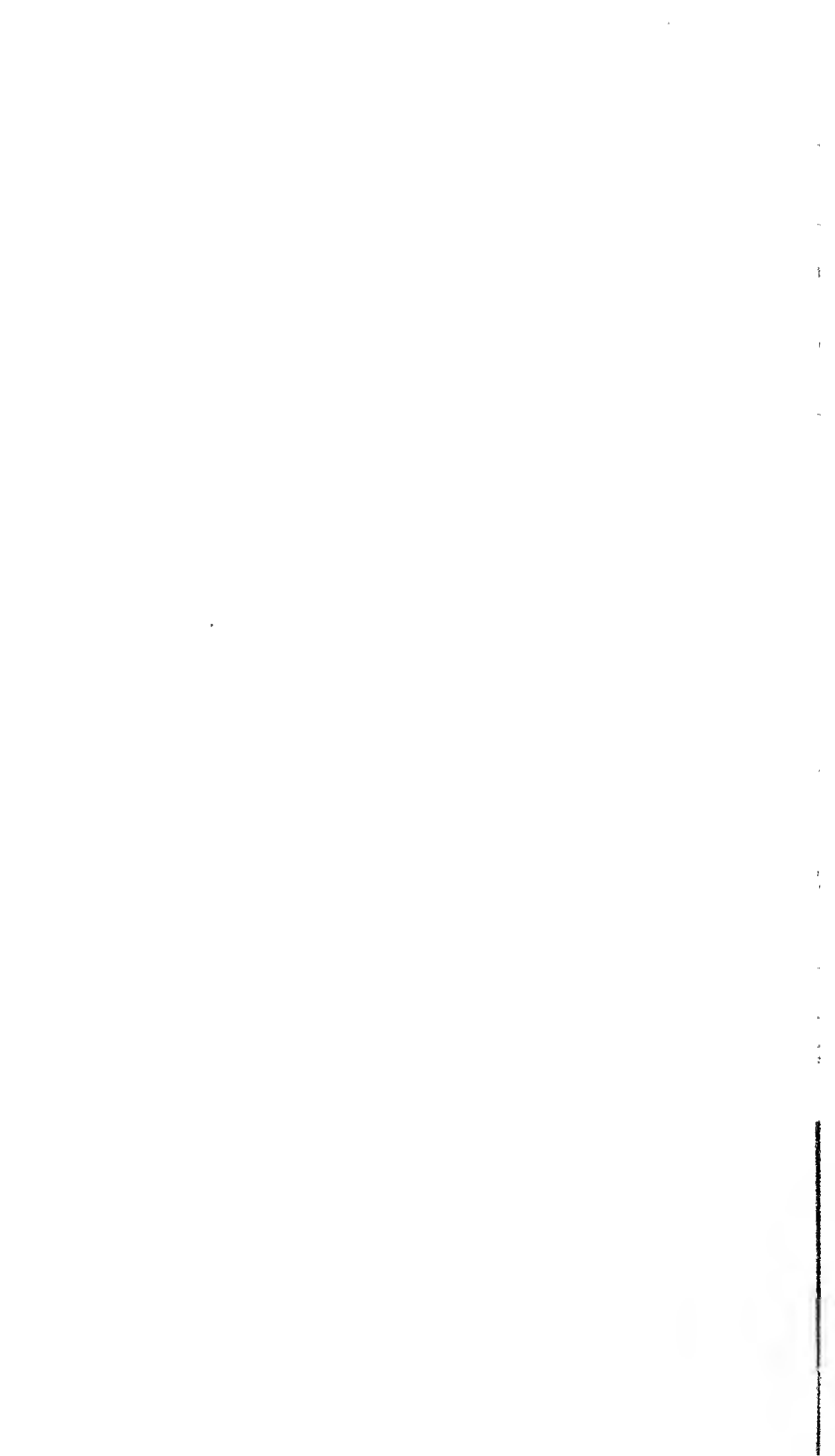
4. The secondary factors are perennial rhinitis, seasonal hay fever, and foci of infection in the sinuses, bronchi, or teeth.

5. The treatment consists of a survey to determine the causative allergens and elimination of them from the environment and the diet, desensitization to the major inhalant allergens, and the elimination of the foci of infection.

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HAY FEVER

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HAY FEVER may be defined as a symptom-complex characterized by periodic sneezing, nasal obstruction and watery discharge, and lacrimation and itching of the eyes and nose, which recurs yearly at a definite season in individuals hypersensitive to plant pollens. This discussion is limited to "seasonal allergic rhinitis," which is a more descriptive term than hay fever and does not concern the perennial form of allergic rhinitis.

Although hay fever has been recognized for several centuries and the name has been in common usage for over one hundred years, it remained for Blackley, in 1873, to demonstrate conclusively that plant pollens were responsible for hay fever. Pollen is probably the most common single cause of sensitiveness. Various estimates suggest from 1 to 2 per cent of all individuals in the United States suffer from pollen allergy at some period in their lives.

Etiology.—Pollinating plants are extremely numerous and of many species, yet few are really significant so far as the production of hay fever is concerned. Thommen¹ has formulated five postulates which must be satisfied by the pollen of any plant in order to be considered of importance in the production of hay fever.

"1. The pollens must contain an excitant of hay fever.

"2. The pollen must be anemophilous, or wind-borne, as regards its mode of pollination.

"3. The pollen must be produced in sufficiently large quantities.

"4. The pollen must be sufficiently buoyant to be carried considerable distances.

"5. The plant producing the pollen must be widely and abundantly distributed."

Careful consideration of these requirements explains why many plants are of no significance in the etiology of hay fever. Most garden flowers, as the rose or goldenrod, are pollinated by insects and hence seldom produce hay fever except by close contact, though the lay opinion is contrary to this fact. The ragweed meets all five demands most satisfactorily and in North America is the most important plant producing hay fever. Wind, rainfall, the amount of sunshine and other climatic conditions influence the concentration of pollen in the air.

The various species of plants which cause hay fever fall into three main groups: trees, grasses and weeds. In most parts of the United States, three distinct hay fever seasons are recognized, these corresponding to the pollination periods of the above three groups. A knowledge of the plant flora of the district in which the victim of hay fever resides is important for proper diagnosis and treatment. Another means of learning which plants cause pollinosis in a given locality is the pollen count. Pollen counts are carried out daily at the clinic during the hay fever seasons. This furnishes valuable information regarding the type and amount of pollen in the air from time to time. It has been found that peaks of pollen production occur coincident with the pollination of certain trees, grasses, or ragweed, and that exacerbations of the patient's symptoms are noted at the same time. The pollen count is much higher after sunny, windy days and quite low following a rainfall.

In the vicinity of Cleveland, the spring (tree) type of hay fever begins during the latter part of April and extends to the middle of June. Spring hay fever is usually mild and is less important than the other types. The chief tree allergens in this district are probably oak, maple, elm, poplar, birch, and sycamore.

The early summer (grass) hay fever season extends from the latter part of May to the latter half of July. A certain amount of overlapping occurs with the tree hay fever season. The grasses are more widely distributed than the trees or weeds, but are less important as a cause of hay fever than are weeds, although they are decidedly more important than the trees. Most authorities concede that timothy is the chief cause

of hay fever among the grasses in Ohio with June grass (*bluegrass*), orchard grass, and red top of less importance. Bermuda and other grasses are of little significance in this section, although they are important elsewhere.

The fall (weed) hay fever season begins about the middle of August and lasts until early October or the first hard frost. Weeds produce more frequent and severe hay fever than the grasses, due to their abundant distribution, rapid growth, and bountiful production of pollen. Short and giant ragweed are the most important plants known to produce hay fever and they are responsible for nearly all cases of fall hay fever in the Cleveland district. Another member of the ragweed family, cocklebur, as well as wormwood, pigweed, lamb's-quarters, Russian thistle, and several others frequently cause reactions to skin tests but are of relatively minor importance as producers of hay fever.

Specific sensitivity to pollens is the only exciting factor of importance in hay fever. It is well to remember that other agents may aggravate the symptoms, however, such as dust, smoke and physical agents.

Hay fever is chiefly a disease of adolescence and early adult life, but frequently it begins in childhood. Heredity has been definitely established as an important predisposing factor. Furthermore, a patient who inherits a tendency to hay fever is most likely to react clinically to the pollen to which he is most frequently and intensely exposed.

Symptoms.—The symptoms and course of hay fever are so well recognized that no description is necessary. Essentially they consist of recurrent attacks of sneezing and nasal obstruction, accompanied by a profuse watery discharge from the nose, and itching, burning, watering eyes. Headaches, malaise, and weakness often occur and, at times, cough and tightness in the chest may warn of an impending asthma. The relative constancy of the date of onset each year is a striking feature of the disease.

The pathologic changes are chiefly a marked edema and cellular infiltration, chiefly of eosinophils, involving the mucous membrane of the nose and accessory sinuses. The eyes are the site of conjunctivitis with chemosis and edema of the lids. Worthy of note is that, in uncomplicated hay fever, there is no

permanent pathologic change but that all manifestations completely clear up in the interval of freedom from symptoms.

Diagnosis.—Investigation of the patient with hay fever is similar to that for other allergic disease described elsewhere in this symposium. A careful history almost always establishes the diagnosis. One should ascertain whether trees, grasses, or weeds are the etiologic agents and often the particular pollen or pollens can be suspected from the history alone. Skin tests are accurate in revealing the offending pollen in almost all cases of true hay fever.

In the *differential diagnosis* of hay fever, the common cold is the chief condition to be considered. As a rule, this causes confusion only with the first one or two attacks of hay fever, as the seasonal recurrence of characteristic symptoms soon distinguishes the latter. If doubt exists, the excessive sneezing, eye symptoms and watery nasal discharge showing an excess of eosinophils characterize hay fever, whereas the common cold begins and ends more slowly and the nasal secretion is purulent with predominance of neutrophils. Perennial allergic rhinitis presents more difficulty in differential diagnosis and may be distinguished from hay fever only by skin tests unless the perennial nature of the symptoms is prominent. The perennial form is usually less severe, especially the ocular symptoms. Certain cases of mold allergy produce a rhinitis with little, if any, perennial nature but the symptoms closely coincide with that of the fall hay fever season. These are often identified only by the skin reactions. Recently I saw a patient who complained of fall hay fever. Skin tests revealed no evidence of sensitivity to pollen but a marked reaction to alternaria. Definite improvement has followed desensitization to this mold. Vernal conjunctivitis is distinguished from hay fever with marked ophthalmic symptoms by the characteristic papillary growths on the conjunctiva, which are permanent and identify vernal conjunctivitis. Skin tests for pollens give negative reactions in this lesion.

Physical examination during the acute stage of hay fever reveals an obstructed nose due to edema of the mucous membrane which is pale and covered with watery secretion. The skin about the nose is frequently irritated, being caused by constant wiping. Conjunctivitis, swollen eyelids, and lacri-

mation complete the picture. The remainder of the physical examination reveals no other findings in uncomplicated hay fever. A thorough examination of the nose and throat is advisable in order to detect physical barriers such as deviated septa, spurs, or polyps. Laboratory examinations are made routinely in all cases of hay fever. These include complete blood counts with differential count, Wassermann reaction of the blood, estimation of the blood sugar and urinalysis. In doubtful cases, nasal smears are taken to determine the presence of eosinophils. A mild blood eosinophilia is often found.

Skin tests to detect the specific pollen or pollens producing hay fever are made routinely by the scratch method. Some allergists recommend testing with the most prominent member of a group, *i. e.*, ragweed, in cases of fall hay fever and for practical purposes this is sufficient. We prefer to make more complete tests for pollens and usually test the pollens of 12 trees, 8 grasses, and 15 weeds, including 3 grains. These tests are usually made on the back unless a high degree of sensitivity is suspected in which case the arm is used. In any event, reactions are carefully watched and the excess pollen quickly removed if the reaction appears rapidly or becomes marked. In this way, constitutional reactions seldom occur. Dilute intradermal tests of varying strengths are sometimes used as they give an indication of the patient's tolerance which is useful in treatment. The size of the wheal with either the scratch or intradermal method is an index of the degree of sensitivity, although the reactivity of the patient's skin and other factors must be taken into account in the interpretation of all tests.

Inhalant and food allergens complete the skin tests. We feel that this is a very important supplement to pollen tests as avoidance of other allergens makes therapy more effective. In a recent article, Clarke and Bolden² state, "Careful study of persons suffering from hay fever will show that the inhalation of substances other than the major pollen, which determines the duration of the symptoms, will greatly aggravate the disease." These inhalant and food tests are done by the scratch method as a rule although, in cases of mild pollen allergy, dilute intradermal tests are sometimes possible. In children too young for direct testing or in cases of eczema or urticaria where a suitable site is not available, indirect tests are often

used with satisfactory results. The ophthalmic test is seldom used but may give useful confirmatory evidence at times. The nasal test may be employed in the rare cases of hay fever where skin tests give negative findings.

Complications.—Asthma is unquestionably the most important complication of hay fever. Statistics vary but probably asthma ultimately develops in from 35 to 50 per cent of all untreated patients with hay fever. Asthma frequently occurs at the end of the pollen season. In many cases, cough and tightness in the chest are found which may later develop into frank asthma. Perennial rhinitis not infrequently accompanies hay fever which seems, in some cases, to be only a seasonal variation of the perennial condition. This is a further argument in favor of complete tests in all patients with hay fever. Occasionally, sinusitis also complicates hay fever.

Treatment.—Treatment of hay fever resolves in most cases to specific hyposensitization to the causative pollen. A few patients are able to avoid contact with the specific pollen by taking an ocean trip or an extended vacation year after year in pollen-free areas. Mechanical filters or air-conditioning for the home will give relief to elderly people or others who may be able to stay indoors for the duration of the pollen season. Economic reasons, however, prohibit these measures for the relief of the great majority of hay fever sufferers. Fortunately, we may now offer them other adequate measures. An encouraging sign is the increasing interest and willing cooperation evidenced by most patients to have adequate investigation of their problem and the institution of specific therapy. A few whose symptoms may be mild are skeptical of treatment and look upon their symptoms merely as a nuisance. The frequent complication of asthma and the tendency in many cases for hay fever to become more severe warrants treatment, I believe, aside from the immediate benefits.

Pollen hyposensitization attempts to increase the patient's tolerance to pollen and to furnish symptomatic relief by the introduction of pollen extract in increasing amounts. The choice of pollens is important when the patient is sensitive to more than one of clinical significance. Fortunately it is not necessary to treat the patient with every pollen extract to which he is sensitive, for certain group relationships exist

among these plants and this simplifies the problem. For example, all the important members of the grass family have a common antigenic relationship. Hence, extract of timothy pollen is employed by many allergists for all the related grasses. Others believe that better results are obtained by using mixtures of varying proportions of the pollens to which the patient shows a reaction. In regard to tree pollens, there is no cross protection between the various families. It is our practice to use a mixture consisting of about 20 per cent oak and about 10 per cent of maple, elm, and poplar, with smaller amounts of several other tree pollens. The grass mixture we use consists of timothy 50 per cent and equal parts of orchard grass, June grass, and red top for the remaining 50 per cent. The weed extract consists usually of equal parts of short and giant ragweed.

The dosage of pollen extract is somewhat confusing because of various methods of preparation and standardization. For a discussion of these methods, the reader is referred to Thomson.¹ We use the following pollen unit of Noon and Freeman: 1 pollen unit is the amount of soluble protein which can be extracted from 0.000001 Gm. of pollen. One Gm. of dried pollen is extracted with 100 cc. of Coca's extracting fluid which produces 1,000,000 units or 10,000 units per cubic centimeter. This is further diluted and supplied to the practitioner in three ampules containing respectively 100, 1000 and 10,000 units per cubic centimeter. The initial dose varies according to the patient's tolerance, but is usually 0.1 to 0.2 cc. of the weakest dilution (10-20 pollen units). Increase in dosage is then made according to a schedule, and is modified according to the patient's reactions, changing to the next higher dilution when 1 cc. is reached.

Certain considerations regarding therapy will bear emphasis.

1. The tolerance of the individual varies so markedly that the dosage of pollen must be adapted to his needs and modified by his reaction. The same treatment is not suitable for every patient.
2. The maximum amount of pollen extract should be administered which the patient can tolerate without severe local

or general reactions. In the average case, we find this is about 10,000 pollen units.

3. Pollen extract is usually administered subcutaneously and as superficially as possible. A tuberculin syringe and 26 gauge needle is suitable for this purpose. The outer aspect of the arm is preferred, the site being low enough to permit application of a tourniquet above the place of injection.

4. Severe local and constitutional reactions are usually avoidable if care be taken in regulating dosage of extract, in reducing the dose of a fresh extract, and by aspirating the syringe carefully to avoid injecting into a vein.

5. Close cooperation is necessary at all times between the family physician and the allergist.

Three methods of hyposensitization therapy are in common use: coseasonal, preseasonal, and perennial.

The coseasonal method may be used in patients who report at the onset of, or during, the hay fever season. The general principle is to give repeated, small doses, increasing them very slowly. The initial dose is about 10 pollen units. Injections are given daily or every second day, according to the patient's symptoms and reactions. Later, the treatments may be extended to three-day intervals but the maximum dosage during the season is about 100 to 300 units.

The preseasonal method is still most commonly used. While we prefer the perennial method, we use preseasonal treatment for many patients who are beginning treatment for the first time and also in a few highly sensitive patients who do not tolerate perennial treatment well. Patients are advised to begin treatment three or four months before the expected onset of the hay fever season. Injections are given at intervals of three to five days and an attempt is made to reach the maximum tolerance before the season begins. The dosage usually reached is about 3000 to 6000 units. With the onset of the hay fever season, the dosage is diminished to about one half the maximum dose reached and then continued at about that level throughout the season. The doses may be slowly increased if no reactions occur and if the patient's symptoms are not relieved but, if the injection causes an increase in symptoms, the dose is decreased still further. As a general rule, it is better

to try smaller, instead of larger, doses if the patient is not improving.

The perennial method of treatment is now advocated by many workers. It attempts to retain the tolerance of the patient rather than build it up afresh each season. After an intensive preseasonal or coseasonal course of treatment, many of our patients continue treatment at intervals of once a week, until the maximum dose is reached (usually about 10,000 units, but this varies considerably). The interval is then lengthened to two weeks or occasionally longer, and treatment is continued at the maximum level until the onset of the next hay fever season when the dose is again decreased to about one half and injections are given once a week. At the conclusion of the season, the maximum dose is quickly regained and treatment lengthened again to intervals of every two weeks. When patients begin treatment more than three months before the anticipated hay fever season, they are at once started on perennial treatment. Injections are given twice a week until the 1:100 dilution is reached, after which they are given weekly until the maximum dose is obtained. In this way, tolerance is built up more slowly than by the preseasonal method.

We prefer the perennial method for several reasons. The seasonal result is as good as by other methods and it offers more hope of a permanent remission of symptoms. Contact between patient and physician is maintained constantly. This is a valuable aid as a perennial rhinitis, for example, may be detected earlier and the patient's general health protected by this close supervision. Intensive preseasonal treatment is avoided and the patient is permitted more time for vacation which often comes just before the fall hay fever season. The only definite disadvantage seems to be a somewhat higher incidence of constitutional reactions but some workers deny this.

A number of patients require symptomatic treatment to lessen their discomfort. Activity should be limited, especially strenuous exercise and fatigue. Contact with pollen should be reduced to a minimum by having the patient remain indoors as much as possible and avoid drafts, train or auto trips, golf courses, and cut flowers. Swimming, diving, and even cold baths are to be avoided. The diet should be light and constipa-

tion should be controlled. Food allergens as well as inhalant allergens should be carefully avoided during the pollen season. Omission of this precaution may result in failure of treatment which would otherwise be successful.

To relieve marked ocular symptoms, dark glasses may be helpful. Eye washes of boric acid or normal saline solution give considerable relief. A solution of adrenalin chloride in normal saline in dilution of 1:5000 or weaker is of much benefit. Milder cases may be relieved by the use of holocaine and adrenalin ointment.

The nasal symptoms may be helped by the use of ephedrine sulfate in doses of $\frac{3}{8}$ to $\frac{3}{4}$ grain or combined with amytal ($\frac{3}{4}$ grain) three or four times daily. We have found that a capsule consisting of phenobarbital, $\frac{1}{2}$ grain, and atropine sulfate, $\frac{1}{200}$ grain, is very useful. Local medication in the nose should be avoided unless it is absolutely necessary. Aqueous solutions of ephedrine sulfate (1 per cent) are frequently tried. The newer, isotonic solutions of ephedrine such as isedrin or glucofedrin seem less irritating. These may be combined with cocaine hydrochloride (1 to 2 per cent), or the latter may be used alone. Cocaine, however, is to be avoided as much as possible. The use of a benzedrine inhaler may give considerable relief.

Passing mention should include change of climate by an ocean voyage to escape tree and grass pollens, or a trip to a hay fever resort to avoid weeds. Mechanical pollen filters or air-conditioning is a useful adjunct to therapy for those who can remain indoors most of the time and to whom expense is a small consideration. Ionization treatment by zinc or other methods has claimed much attention recently. The opinion of the best informed seems to be that present results do not warrant its use.

Results of therapy are extremely variable. Spontaneous remissions are rare in patients who have had the disease only a few years. Satisfactory results are more easily obtained in cases of hay fever due to trees and grasses than in the type due to weeds. Tuft³ recently stated "satisfactory results varying from partial to complete relief may be expected in 85 per cent of all patients, and poor results or failures in the other 15 per cent." The duration of treatment is important to the patient

and is a question difficult to answer. Certainly it will usually be necessary for at least three years as few patients obtain permanent remission in less than three years: many require five or six years and others even more.

SUMMARY

The method of investigation of the patient with hay fever has been detailed. Treatment has been discussed and our preference for the perennial method outlined. The necessity for complete investigation of the patient is stressed.

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CONTACT DERMATITIS

GEO. H. CURTIS

LOCAL SKIN HYPERSENSITIVITY OF SKIN ALLERGY

It is the purpose of this section of the symposium on allergy to present briefly the principal evidence that has established contact dermatitis as a manifestation of allergy and to describe a useful routine procedure for the clinical investigation of cases of contact dermatitis. Armed with the knowledge that each of the hundreds of substances that may be brought into contact with the skin excites the same fundamental allergic mechanism manifested by the same eczematous reaction, the physician is prepared to ferret out the offending substance and, by removing it from the contact with the patient or the patient from his contact environment, cure the dermatitis.

Theoretically, therefore, the causal agent in every case of contact dermatitis can be discovered and eliminated; however, in actual practice this is not always true and the more difficult problems demand a thorough, painstaking history aided by good "detective" work. In most instances, the dermatitis is seen early and, if it is recognized and sufficient time and thought are devoted to the problem, a successful solution is obtained. After months or years of repeated exposures, the original character of the dermatitis will have changed and the patient in all probability will have acquired hypersensitiveness to a number of substances. In such instances, to recognize the dermatitis, find the troublesome irritants, and evaluate them in relation to cause and treatment become exceedingly difficult. To complicate matters further, the skin may reach a state of such hyperirritability that a minimal amount of irritation may precipitate repeated exacerbations, so that the dermatitis continues long after the primary irritant or irritants have been removed. A careful history, coupled with the proper use of the patch test, will reduce the number of these "hopeless" cases to a minimum.

A discussion of the industrial dermatoses will not be attempted because the subject is much too large and specialized. According to Foerster,¹ "The United States Department of Labor lists 928 hazardous occupations including 122 of the more common activities in which skin diseases are prone to develop." In general the search for the offending substances is conducted in the same way as for any nonindustrial contact dermatitis except that a detailed knowledge of the worker's industrial environment and a full cooperation on the part of the company are necessary. Downing² has written excellent articles and Schwartz³ has submitted a monograph on the industrial dermatoses.

MORPHOLOGY AND SUBJECTIVE SYMPTOMS

Typical contact dermatitis is characterized histologically by spongiosis and vesiculation within the epidermis and clinically by erythema, edema, papules, vesicles and later lichenification, infiltration, and scaling. The eruption is polymorphic in its manifestations, varying from a mild erythema to gangrene.^{4, 5} Usually, acute, subacute, and chronic stages are distinguished, but the severity and morphology of the dermatitis in these stages are modified somewhat by the location and the degree of hypersensitivity of the individual. The finding of vesicles is important and they are almost always present.

In the early stages, the erythema is limited to the area of contact. This is shortly followed by edema, swelling, vesiculation, and crusting. Bullae may develop. Mild stages of erythema and papules only are sometimes seen. The acute erythema-vesicular dermatitis may become secondarily infected, resulting in pus-filled vesicles and pustules. In the subacute stages there is a minimum of vesiculation, the erythema usually is less pronounced, and scaling is more prominent. The skin may be slightly infiltrated, the epidermis somewhat thickened and glossy, and the tiny epidermal sulci magnified.

The chronic stage is identified by lichenification of the epidermis, infiltration of the corium, and scaling. The skin in the areas of greatest exposure is leathery, rough, covered with small adherent scales, and the color is somewhat grayish-tan.

During the acute and subacute forms, the dermatitis, in some instances, spreads from the original areas of contact and

over a period of several weeks new areas continue to develop and involve a large part of the cutaneous surface. These may vary from an erythematous blush extending for some distance away from the area of contact to a generalized dermatitis closely simulating an exfoliative dermatitis. If some of the substance (such as mercury, quinine, chrysarolin, etc.) is absorbed, a dermatitis medicamentosa may follow.

Pruritus almost always accompanies eczema, usually preceding the eruption from a few minutes to several hours. It may be mild or intolerable. If the patient cannot refrain from scratching excoriations, ruptured vesicles, and bullae, bleeding surfaces and pyoderma are the rule. At the height of the vesiculation, the itching has practically disappeared. In some instances, it is replaced by pain of varying degree or by smarting or burning sensation. Bray⁶ has outlined the pathological physiology of pruritus.

ALLERGY IN CONTACT DERMATITIS

American authors use the terms "dermatitis venenata," "contact dermatitis," and "occupational eczema" to designate the same dermatosis, while in Europe it is spoken of as eczema. Dowling⁷ defines eczema (contact dermatitis, dermatitis venenata, etc.) as "a complex reaction of the skin of certain predisposed subjects, first, to agents that are not at all irritating to normal skins; second, to agents that damage even the normal skin but which, under daily contact, produce ordinarily a mild degree of roughness, transient redness or no reaction at all. There are two broad groups of contact dermatitis: first, hypersensitivity to a vast number of chemical substances with eczematization occurring within a few days to years of contact. In susceptible persons these normally nonirritating substances excite an eczematous reaction in high dilution and sometimes a very first contact will produce a dermatitis. The second group is due to 'universal irritants.' Eczema develops after prolonged exposure to the substances." This definition includes the so-called "idiosyncrasies" as well as acquired hypersensitivity.

That hypersensitivity in contact dermatitis is acquired and not inherited has been demonstrated by both statistical and experimental studies in hypersensitivity to poison ivy and other plants. Practically no infants, regardless of family history of

atopy, are hypersensitive to poison ivy extracts but hypersensitivity may be induced by repeated applications of the extracts to the skin. The percentage of individuals hypersensitive to plants increases with age to something like 65 per cent of all adults.^{8, 9, 10} Heinbecker¹¹ was unable to demonstrate hypersensitivity to *Rhus toxicodendron* among the Eskimos. The reason for this lies in the fact that Eskimos inhabit regions beyond the most northern limits of *Rhus* vegetation. On the other hand, hypersensitivity to *Rhus* is common among their cousins, the American Indians.

Bloch,¹² in his studies on primrose dermatitis, has shown that there is no difference in the mechanism between idiosyncrasy and acquired hypersensitivity. He was able to induce such a high degree of sensitivity in himself that to walk into a room containing a primrose plant (in bloom) was sufficient to produce a severe dermatitis. He was not able to demonstrate a positive passive transfer.

Haxthausen¹³ injected intracutaneously solutions prepared by mixing mercuric chloride, formalin, and chromic acid with horse serum. After a period of twelve to fourteen days, positive patch tests with 1 per cent solutions of the chemicals were obtained at the sites of the injections. Similar experiments with mixtures of the above chemicals and yeast cells and staphylococci were successful in 3 out of 14 cases. Iodoform, iodine, quinine, turpentine, and paraphenylenediamine used in the above experiments gave negative results. In the successful experiments, antigen-antibody reactions could not be demonstrated, *i. e.*, passive transfer tests. Block and Peter¹⁴ transplanted the skin of a person hypersensitive to iodoform to a normal individual. They found on repeated testing that the transplanted skin remained hypersensitive to iodoform when taken internally or applied externally while the person's own skin remained normal. These experiments demonstrate that the reaction takes place in the fixed cells of the epidermis.

Further studies have determined a chronology of development of the eczematous reaction.^{8, 15, 16}

1. A period of refractoriness to sensitization ending with the beginning of the process of sensitization. The time is from zero to many years.

2. A period of incubation of sensitivity. This corresponds

to infectious diseases and diseases such as crum sickness, experimental arsphenamine dermatitis, and anaphylaxis. The time is from nine to fourteen days.

3. A period of reaction time—eighteen to seventy-two hours. This corresponds to the reaction time of the allergic infectious diseases such as tuberculosis, lymphopathia venereum, mycoses, and the delayed reactions in atopy.

In the past six or seven years, laboratory animals have been sensitized to the oil extracts of poison ivy, ragweed, and primrose.^{17, 18, 19, 20} The papers of Sulzberger and Goodman²¹ and the excellent paper of Sulzberger²² have summarized the present knowledge of allergy in dermatology. Table I reproduces that part of their summaries directly related to contact dermatitis.

CLINICAL INVESTIGATION OF CONTACT DERMATITIS

The evidence that contact dermatitis is a manifestation of allergy has separated this dermatosis from the group of eczematoid dermatoses about which little is known and placed

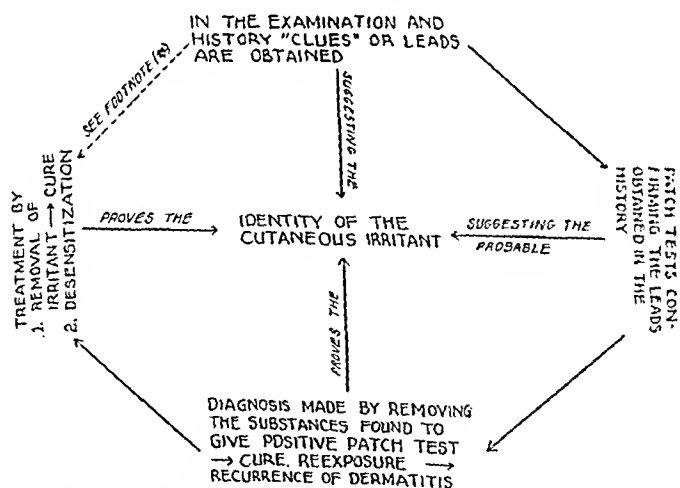


Fig. 43.—Diagram showing the relation of the examination and history, patch test, diagnosis and treatment of contact dermatitis to the identification of the external irritant.

* The aberrant dotted vector represents those cases in which the identity of the irritant is so obvious that, from the practical time-saving viewpoint, the direct elimination of the indicated irritant without the time-consuming

it among those having a definite clinical entity. The etiology, symptoms, signs, pathology, methods of diagnosis, prognosis, and treatment are correlated. From the etiologic standpoint, if contact dermatitis were produced by a single cause such as we find in the infectious diseases, its management would be relatively simple, but a great many substances are capable of producing the same cutaneous reaction and, in order that every case may be properly managed, the identification of the irritant or irritants is of prime importance. This fact is the hub about which the history, patch test, diagnosis, and treatment revolve. Diagrammatically this would be represented as shown in Fig. 43.

(A) EXAMINATION AND HISTORY

Probably the best procedure to follow and one which most dermatologists employ is to examine the cutaneous surface first. Because a large number of skin diseases are diagnosed at sight, the number of dermatoses that may be confused with contact dermatitis is immediately reduced to a few. Furthermore, the examination of the cutaneous lesions enables one to keep the patient's history in the right direction since most patients do not relate their trouble to an external cause but ascribe its origin to "too much acid" or "something in the blood." Therefore a careful inspection as to the nature and distribution of the dermatitis is important. The former has been described under the section on morphology, and the latter is most conveniently placed among the "clues" taken up in the history as obtained from the patient.

Too much emphasis cannot be placed upon the importance of the history in contact dermatitis, as it is of the greatest practical help in finding the cause and far exceeds the value of the information obtained by skin tests. If a tentative diagnosis of contact dermatitis is made, the nature of the trouble is explained to the patient, and his cooperation is obtained, the

intermediate diagnostic procedures is sufficient, but the physician must not lose sight of the fact that, from the scientific viewpoint, this is untenable because the ingredient in the cosmetic, jewelry piece, clothing, medicament, etc., that produced the dermatitis should be identified and made known to the patient in order that he may be protected from future contact with the chemical that may be incorporated in other preparations.

history is facilitated for, in some instances, a detailed inquiry must be made into the patient's most intimate habits, routine, and environment. The points of inquiry about the patient's family and personal history are listed in Table 1.

In the examination of the skin and history, certain clues or leads may be brought to light which, when followed up by the patch test, lead to the discovery of the irritant. For practical purposes they may be conveniently but not sharply divided into the following three groups:

Group I.—Clues or leads of a general nature relative to the environment, leading to the discovery of the cause of a disseminated dermatitis of the exposed areas:

- (a) The exposed parts of the cutaneous surface are usually the sites of predilection and, at times, are associated with involvement of the genitalia.
- (b) The chronology of the appearance of the eruption.
- (c) Seasonal occurrence of the dermatitis is important in plant dermatitis.
- (d) The effect that absence from the usual environment may have on the course of the dermatitis.

These four points are brought out in the following case reported by Odland.²³

A seventy-year-old woman had had eczema for five years. This was located on the hands, forearms, legs, ankles, and feet. It first appeared on the hands and gradually involved the forearms to the elbows. It occurred in May and disappeared late in September of every year. Further questioning brought out the fact that, for a few weeks during July, the patient visited relatives in the city. During this time the dermatitis began to clear up but did not entirely disappear. On her return home, it became worse than ever. The itching was so severe that the patient could not sleep and she took to walking barefoot in her yard. The fact that the eczema did not occur on the feet, ankles, and legs until after she began to walk barefooted in her yard gave the important clue that the dermatitis was probably due to weeds. Patch tests were made with the common weeds known to produce a dermatitis. The test with fennel gave a positive reaction.

(e) Nonseasonal periodic exacerbations or recurrences. The classical example of this is the "Sunday dermatitis,"²⁴ following the handling of the rotogravure section of the Sunday paper. The para-red dye in the ink has been found to be the cause. Another example is the case described by Engman.²⁵

TABLE 1*
DIFFERENTIAL CHARACTERISTICS OF COMMON ALLERGIC DERMATOSES

Contact dermatitis.	Atopic dermatitis.	Drug eruptions.	Fungus dermatitis—eczematous dermatophytids.
1. Epidermis is "shock tissue" and practically always only tissue affected.	Blood vessels in cutis "shock tissue." Capillary permeability and smooth muscle spasm.	Deep cutis, cutis epidermis and follicles are "shock tissue."	Upper cutis, cutis.
2. Rarely a family history of asthma, hay fever, atopic dermatitis. If these are present, it is coincidental.	Family history of asthma, hay fever, and perhaps migraine or urticaria.	Same as contact dermatitis.	
3. Lack of personal history of (2).	Personal history often reveals some of those under (2).	Same as contact dermatitis.	
4. Eosinophilia rarely demonstrable.	Eosinophilia in blood smears.	Eosinophilia in blood smears.	
5. Scratch and intracutaneous skin tests— <i>negative</i> .	Scratch and intradermal tests— <i>positive</i> .	In rare urticarial eruptions the scratch or intracutaneous tests are <i>positive</i> .	Intracutaneous or patch test.
6. Passive transfer— <i>negative</i> .	Passive transfer— <i>positive</i> .	Same as contact dermatitis.	
7. Relief on removal of offending substances.	Same.	Same.	May be desensitized by fungus extracts.
8. Recurrence or exacerbation on exposure.	Same.	Same.	Recurrence on reinfection.

CONTACT DERMATITIS

<p>9. Identification of offending substances by reproduction of eczematous reaction to patch tests. Reaction time, twenty-four or more hours.</p>	<p>Offending substances cannot be identified by patch tests. Reaction time five to thirty minutes.</p>	<p>Patch tests usually reproduce the eczematous reaction in eczematous drug eruptions (identical with contact dermatitis) but rarely reproduces the morphe of the dermatosis in acneiform or vegetating drug eruptions (Dermatitis medicamentosa.) Reaction time, one minute to days.</p>	<p>Intracutaneous or patch test is specific but not diagnostic.</p>
<p>10. Presence of purely epidermal lesions—erythema, edema, vesicles (to bullae) papules, histologic spongiosis.</p>	<p>Presence of capillary permeability. Papules, lichenification and oozing. Vesiculation absent.</p>	<p>Lesions often characteristic for offending drug. Bromides and iodine cause acneiform, vegetating or nodular-like and erythema-like eruptions. Phenolphthalein, antipyrine, amidopyrine, etc., produce fixed drug eruptions.</p>	<p>Vesiculation usually in upper cutis and cutis. Larger than those of contact dermatitis. Frequently the two are indistinguishable.</p>
<p>11. Causal substances are allergens but not antigens or atopens—rarely protein but are chemicals, metallic salts, anesthetics, dyes, etc., or plant oils or products of fungi and bacteria.</p>	<p>Causal substances are atopens or reagins, or antigens but not precipitins. Usually foods, inhalants (powders, dusts, animal emanations, spores of fungi, plant pollens, etc.). Clothing (silk, wool and fur), etc.</p>	<p>Allergens but not atopens or antigens.</p>	<p>Allergens: fungus products (thyromycetes and molds.)</p>

* Tabulation of data taken from Sulzberger and Goodman²¹ and Coxa and Sulzberger, cited by Briv.

This was the unusual case of a man in whom an acute edematous, erythematous, vesicular dermatitis of the face developed periodically. In the beginning, the dermatitis was limited to one side of his face, but later both sides were involved. No clue as to the cause of the dermatitis was obtained in his history. One day he came to the office with a new attack. He was accompanied by his wife, and it was noticed that her hair was bleached. On further questioning both recalled that the patient's trouble occurred the day after his wife had applied the hair bleach, and he was accustomed to resting his cheek against her head at night. The patient had no further trouble after his wife stopped using the hair bleach.

(f) Contact with substances that are used by others with whom the patient is closely associated. This point at times necessitates a careful inquiry concerning every member of the household, and should be kept in mind during the investigation of every case in which the cause is obscure. In addition to the preceding case report, a dermatitis from vectors may occur. A case of this kind is reported by Sulzberger and Kerr:¹⁵

A woman had a recurrent, erythematous, vesicular dermatitis of her left arm and scaling dermatitis of her right hand. There was no contact history except that she stated that it appeared shortly after doing the family washing. This suggested soaps, powders, etc., but patch tests with these were negative. Further questioning revealed that her daughter had been using Mazon ointment for athlete's foot. The patient gave a positive patch test to Mazon.

(g) Hobbies should be investigated in obscure cases. Senear²⁶ reports the following case:

Periodically during the summer a business man had a dermatitis which first appeared on the hands and later on the forearms, face, neck, and finally the popliteal spaces became involved. During one summer he changed his address for some weeks and the dermatitis cleared up, but recurred shortly after his return. On inquiring into his activities during the few days preceding the onset of the dermatitis, it was learned that he was an archery enthusiast and had been cleaning his bow. The bow was made of English yew and a patch test with the moistened wood scrapings gave a positive reaction. Tests with the dry shavings gave a negative reaction.

The author discusses in detail dermatitis due to various woods and their ingredients.

Sportsmen, such as golfers, come into contact with leather bags, leather on clubs, and of course, weeds: horsemen—leather and stable materials: motorists—gasoline, oil, cleaning

solutions, polishes, upholstering, varnishes; gardeners—plants and weeds; musicians—wood and rubber mouthpieces, polishes; violinists—resins, glue and varnish. These are a few of the numerous hobbies in which various substances that people handle may cause a dermatitis.

(h) In the home, contact with numerous substances that may produce a dermatitis must be determined. Chemicals such as bleaches, turpentine, naphtha, camphor, benzine, and phenol are listed as well as soaps, laundry powders, insecticides, moth sprays, furniture and floor polishes, varnishes, lacquered pieces, upholstering, plants, pets, housedust, and medicaments in the medicine cabinet. Kile²⁷ describes an interesting case of dermatitis due to goat hair in the mohair upholstering of furniture:

A traveling salesman had had a recurrent, chronic, scaling, lichenified dermatitis of the face, arms, hands, and legs for twenty years. It was not seasonal and exacerbations occurred both at home and while traveling. The dermatitis was thought to be due to contact dermatitis because of its nature and distribution and the lack of family or personal history of allergy. He was given patch tests with all the common excitants including housedust oil which was positive. This led to patch testing with all the materials in the home which produced lint and a patch test with the mohair upholstery gave a positive reaction. Further tests with the ingredients of mohair revealed that the patient was sensitive to goat hair. This explained the exacerbation of the dermatitis while the patient was traveling, since goat hair is used in all sorts of upholstery. The patient was desensitized by extracts of the goat hair and he was able to follow his usual routine fairly comfortably.

Niles²⁸ reports a case of contact dermatitis of the arms, hands and face due to a card table cover.

(i) The patient's occupation is important among the leads obtained in the history. With the exception of the industrial eczemas, the following is a list of only a few of the nonindustrial occupations and professions in which contact dermatitis occurs together with the most common irritants: Dentists—local anesthetics, rubber bases in false dentures, amalgams, rubber gloves; physicians and nurses—anesthetics, rubber gloves, sterilizing solutions of various kinds, instruments, tincture of green soap, medicaments; photographers—developing solutions; lithographers—blue print markers, sodium bisulfide; printers—inks and cleaning solutions which usually contain

chromium salts; beauticians—creams, hair dyes and bleaches, wave sets, formaldehyde, shampoos; barbers—various hair tonics and sterilizing solutions; florists—plants, flowers; bakers²⁹—flour and chemicals; jewelers—materials used in cleaning and refinishing jewelry; cement workers—cement, lime, sulfur, lime water; painters—turpentine, paint thinner, naphtha, thinning oils; carpenters and cabinet makers—woods, glue; violin makers—resins, varnishes, glue; brick makers—clay sprays; business men—ear phones and telephone and mouthpieces and dictaphone cylinders³⁰; school teachers—colored chalk, chemicals; service station attendants and garage mechanics—gasoline, oils, greases, paints and ointment applied to hands for protection against the former chemicals. An example of the protective substance itself producing a dermatitis is one which we observed recently:

A garage mechanic, forty years of age, came to the clinic on August 5, 1937, complaining of a dermatitis of the dorsa of his hands. He had had this continuously for six weeks. The dermatitis was limited to the dorsa of the fingers and hands and consisted of erythematous patches of vesicles and crusting. The hands were swollen. The dermatitis first appeared on the left hand. Previous to the onset of the present eruption, the patient had known that gasoline irritated his hands and by avoiding gasoline as much as possible he was able to prevent severe exacerbations. He then began to use "Protex" as a protection against oil, grease, and gasoline, but his hands from that time developed a dermatitis of gradually increasing severity. Patch tests with the Protex and dilute solutions of gasoline were positive. The mechanic went back to wearing gloves and avoiding gasoline and the Protex and has been almost entirely free of the dermatitis.

Many other occupations may be listed but space obviously does not permit. Weber³¹ and Laymon³² have published complete lists of the various occupations in which contact dermatitis may occur as well as all the known irritants.

(j) A detailed and chronologic listing of the various lotions, ointments, antiseptics, etc., that have been used in previous treatment is an important lead. Practically every drug used in dermatologic therapy is capable of producing a dermatitis. Some ingested drugs such as quinine, resorcin, urotropin, mercury, etc., will cause a dermatitis medicamentosa that can be detected by the patch test.

(k) The fact that photosensitization* may be a factor in the production of dermatitis of external cause should be kept in mind. The so-called berlock dermatitis, a peculiar pigmented dermatitis caused by exposing those surfaces to which eau de cologne and perfumes have been applied to sunlight, is an example of dermatitis due to photosensitization.³⁴ An interesting example of the effect of sunlight on producing a plant dermatitis has been reported by Cummer and Dexter:³⁵

A white man had suffered an eruption on the forearms which had occurred in the summer for two years. Two days before examination, he had trimmed the plants in his garden and carried the trimmings on his forearms. He wore gloves. The dermatitis consisted of patches of irregular sizes and shapes in which the skin was dusky red with an occasional bean-sized blister. There was little or no itching or burning. On subsiding, a residual pigmentation lasted for months. Patch tests with all the flowers, leaves, and stems of the plants in his garden were negative. The authors were at a loss to account for the dermatitis until the patient recalled that once the plant had brushed his forehead and forty-eight hours later a dermatitis appeared there. This suggested a dermatitis similar to berlock dermatitis. A pod was rubbed on his forearm and exposed to the sunlight and a vesicobullous dermatitis developed in sixteen hours. Another place to which the pod was rubbed which was shielded from the sunlight gave a negative reaction.

(l) An interpretation as to the relation of the primary irritants to contact dermatitis sometimes is important. Strong acids, alkalis, escharotics, rubefacients, strong cleansing powders, soaps and fluids, grease removers, gasoline, turpentine, benzene, kerosene, and the like are considered primary irritants.

These irritants, when applied to the skin in sufficient concentration, produce a simple dermatitis or burn. Their relation to hypersensitivity has been discussed. Of these, the universally used soaps are probably the most difficult of interpretation. Jordon, Walker and Osborne³⁵ studied the eczematizing properties of 8 popular brands of toilet and laundry soaps and concluded that, if a soap is suspected, it should be

* At the present time, no direct evidence has been offered to show that this form of dermatitis is due to allergy, but since this as well as dermatitis due to the primary irritants must be considered in the investigation of contact dermatitis, it is placed here. However, the fact that the ingredients of some of these substances can and do produce an eczematous reaction without photosensitization should not be forgotten.

tested in dilutions of 1:400 to 1:100 and that a mild erythema at the site of the test should be disregarded. They have listed the ingredients of the various soaps that commonly produce a dermatitis.

(*m*) A knowledge of a large number of irritants and their composition is valuable.^{31, 32}

Group II.—Clues or leads suggesting certain causal agents which produce a dermatitis on local areas of the exposed surfaces, although all of these areas may be involved at the same time.

(*a*) Scalp and face. A dermatitis of these areas suggests sweat band of the hat, hair dyes, bleaches and tonics, shampoos, wave sets, cosmetics including creams, rouge, powders, powder bases, toilet waters, perfumes, etc.³⁶

(*b*) Eyelids and about the eyes and nose: eye shadows, eyelash dyes, mascara, eyelash curlers, and other cosmetics, spectacle frames, eyewashes, eye medicaments and nasal sprays are suggestive causes. Rattner³⁷ reports 4 cases of dermatitis of the eyelids in which one was caused by a new jar of a cream of the same brand that the patient had been using for years. This suggests the possibility that the manufacturer had changed some of the ingredients.

(*c*) Ears: toilet waters, perfumes, ear rings, spectacle frames.

(*d*) Lips: lipsticks. The lips may be involved as a part of a dermatitis involving the mouth.

(*e*) Mouth: tooth pastes and powders, mouth washes, rubber compound dental plates, chewing gum, etc.

Netherton³⁸ has recently reported a dermatitis due to a tooth powder involving the gums, lips, hands, and fingers:

A young lady came to the clinic in July, 1937, complaining of a sore mouth and hands. For three months she had had a dry, thickened, scaly plaque which was limited to the left palm. Three days prior to her visit to the clinic, a stomatitis and an eruption involving the lips and skin about the mouth and on the lateral surfaces of the fingers of the right hand developed. The gums were raw and bleeding, and an acute erythematous, vesicular dermatitis was present about the mouth and on the fingers of the right hand. While brushing her teeth some of the fluid containing the powder trickled down the fingers of the right hand. Examination of scales from the lesions in the left palm were negative for fungi. Her feet did not show any signs of an epidermophyton infection. A patch test with the tooth powder applied to the forearm

was positive. The eruption and stomatitis disappeared with cessation of the use of the tooth powder.

This case illustrates several interesting points. First, the dermatitis is modified by its location—in this case the palms, gums, glabrous skin each exhibited a dermatitis, different in appearance. Second, a dermatitis developing in widely separated areas can be correlated by chronology of appearance in the search for a common irritant—in this case the mouth, palm of one hand and the fingers of the other. Third, in the study of the case it was found that patch tests with the separate ingredients were negative, but when they were added together a mild erythema occurred at the site of the test. The ingredients could not be mixed according to the manufacturer's formula, because it was unknown to us, but repeated tests with the powder sent directly to us by the company were strongly positive. This suggests the possibility that a chemical reaction took place between the ingredients of the powder with the formation of a new chemical compound which produced the hypersensitivity and dermatitis. Schwartz and Hocker³⁹ described a dermatitis among telephone linemen who handled cables and found it to be due probably to the heat decomposition of the dyes.

(f) Neck and face: furs, fur coat collars, fur dyes, scarfs, necklaces, and other jewelry are common causes of a dermatitis in these regions in addition to those affecting the scalp and face. Although it has no direct bearing to contact dermatitis I do not believe it is out of place to mention, for the reason that large pendants and necklaces are coming back into fashion, the peculiar and interesting cases of pseudoleukoderma appearing on the neck and upper chest as a result of large necklaces and pendants shielding certain surfaces from the sun, thereby producing patterns whose outlines coincide with those of the necklace or pendant. The surrounding skin is simply suntanned while the skin underneath the pieces retains its normal color.⁴⁰

(g) Hands, wrists, and forearms. The large majority of cases of contact dermatitis involving the hands occur among industrial workers and among the nonindustrial trades and professions a few of which were listed elsewhere. To enumer-

ate the list of irritants affecting the hands would be a repetition of Weber's list. We have found that it is of value in tracing the irritant to have the patient keep a diary of the materials that he may handle from day to day. Gloves should head the list.

Although the fingers, wrists and forearms are usually involved in a dermatitis of the hands, localized areas of dermatitis on these parts suggests wrist watches and bands, bracelets, cuff links, rings, and clothing. Higoumenakis⁴⁰ records a case of dermatitis localized to a small area in the lower third of the forearms. This was due to aluminum cuff links. Patch tests with the links and other aluminum salts gave positive reactions.

(h) Ankles: the ankles are usually considered as exposed parts. Plants and weeds are the most common offenders. However, they may be involved in a dermatitis due to socks and shoes.

Group III.—Leads or clues leading to the discovery of the irritants usually affecting the "covered areas" of the cutaneous surface. As stated before, the covered areas may be involved in a generalized dermatitis resulting from the generalized hypersensitivity to a substance that comes into contact with the exposed surfaces.

(a) Axillae: depilatories, deodorants, perspiration shields, silk and wool and rayon clothing are common offenders. We have observed many cases of dermatitis due to these substances. A case reported by Netherton³⁸ is illustrative:

A woman in good health but troubled with hyperhidrosis for several years came to the clinic with a subacute, erythematous, vesicular and crusted dermatitis of the axillae which had been present for two months. Each axilla was surrounded by a fairly well demarcated dermatitis (Fig. 44). The skin in the axillae showed only a few small areas of dermatitis. The feet and groins were free from epidermophytosis. Scales from the axillary lesions were examined for fungi and none were found. A mild zinc oxide ointment had been used without benefit. The nature and distribution of the lesions suggested contact dermatitis. The history revealed that she was accustomed to wearing perspiration shields to protect her clothing from excessive perspiration. Patch tests with the rubber and cloth covering of a new unwashed shield and an old washed shield revealed positive reactions to the parts of the new shield. The patient was advised to thoroughly wash the new shields before using them or use a different kind. Since she has not returned, it is assumed that she followed instructions and had no further trouble.

Ringworm of the axillae must always be considered as a possible cause of dermatitis in these areas, but occasionally the two will occur together.

(b) Abdomen and thighs: these regions are the usual sites of a dermatitis caused by materials carried in the pockets. Match and match-box dermatitis is the classical example.



Fig. 44.—Contact dermatitis due to perspiration shields of dresses. Note the sharp border and relatively clear central part closely resembling *tenia corporis*. (Netherton)

The dermatitis usually is localized to an area underlying the pocket (shirt, vest, trousers, lounging robe, etc.).

An interesting case is reported by Anderson and Brunsting.⁴²

A chemistry teacher for the preceding nine years had suffered from a dermatitis every autumn and winter. When he was seen during an acute flare up, there was erythema and edema of the face and eyelids and an erythematous-papular eruption of the right thigh in the region of the right trouser pocket. The history pointed to a chemical which he handled in his laboratory

during the school term. Patch tests revealed positive reactions to mercury and its compounds. The patient then recalled that the dermatitis always appeared following experiments with mercury. Mercury-covered coins were found in his right hand trouser pocket.

(c) The buttocks are the usual site of a dermatitis due to girdles and stained toilet seats. Odland's case²³ is representative of "toilet-seat dermatitis."

A white man, fifty-seven years of age, sought advice concerning a dermatitis on his buttocks. On examination, a narrow band of dermatitis 2 inches wide was seen to extend all the way across the buttocks. The location of the dermatitis suggested something he sat on. The history brought out the fact that he had recently purchased a new toilet seat finished with a red stain. On patch testing, a positive reaction was obtained to the scrapings from the seat.



Fig. 45.—Dermatitis due to a stained and varnished toilet seat

We have had several similar cases, but the dermatitis has formed a ring involving the buttocks and the lateral and posterior aspects of the thighs (Fig. 45).

(d) Genitalia and perineum: the genitalia are frequently involved in association with a dermatitis of the exposed areas more frequently in the weed and plant eczemas and by liquid

and dust irritants. The majority of cases, however, are the result of medication to the parts. Douches, suppositories, contraceptives, rubber condoms, and numerous medications are offenders. Mitchell¹³ describes the following case:

A cosmetic manufacturer was treated with anal suppositories for hemorrhoids. In a few days the anal trouble became worse and a physician told the patient to stop using the suppositories whereupon the dermatitis cleared up. On two other occasions the patient used the suppositories and each time the itching and soreness of the perineum returned. Examination showed an erythematous, vesicular dermatitis about the anus and extending over the buttocks. The suppositories were analyzed for resorcin according to the U. S. Pharmacopoeia and the tests gave positive reactions. Patch tests with resorcin and the suppositories gave positive reactions. Positive tests were also obtained with hydroquinine, pyrocatechin, hexylresorcinol, and euresol which are related to resorcin. This case also illustrates hypersensitivity in contact dermatitis to a group of allied chemicals.

(e) Thighs and legs: occasionally a dermatitis is seen on the thighs and calves in the regions where the metal parts of hose supporters touch the skin.

(f) Eczema of the feet and ankles suggests socks, shoe leather, leather dyes, and freshly dyed shoes. Schwartz¹⁴ has described a detailed method by which each of the materials, dye, and finish of socks may be determined to be the cause of an eczema due to socks. From a practical standpoint, a patch test with the material of the unwashed socks is all that is necessary. Sulzberger and Kerr¹⁵ reported a case of dermatitis of the feet in which contact dermatitis and ringworm were superimposed.

A young man had a severe vesicular eruption on the fingers, palms, and dorsa of the hands, and a similar dermatitis on the ankles and feet. Fungi were found in the scales from the feet and a diagnosis of dermatophytosis and a dermatophytid eruption of the hands was made. The patient was treated for the fungus infection and desensitized with fungus extracts. The hands cleared up entirely, but the dermatitis of the feet and ankles persisted. Further history revealed that the patient could not wear leather wrist watch straps because it irritated his skin. Patch tests with leather from the patient's shoes gave positive reactions.

This case illustrates the point that one dermatosis may be superimposed on another, the one affording a portal of entry to the other or to a multiple hypersensitivity to other irritants

or to fungus extracts (dermatophytid). Haxthausen¹³ has reported experiments on this phase. We have had a case of dermatitis due to the socks the patient wore (Fig. 46).

(g) A dermatitis of the covered surfaces may be generalized and unless it is a part of the generalized dermatitis from an irritant acting on the exposed areas, it is most likely to be due to an article of clothing that involves most of the trunk and extremities. Bonnevie and Genner⁴⁵ report 15 cases of eczema



Fig. 46.—Dermatitis due to navy blue rayon socks.

due to dyed clothing. Netherton³⁸ reports a case of dermatitis due to clothing and involving several covered areas:

A white woman, sixty-six years of age, came to the clinic complaining of an eruption on her trunk and thighs. This first appeared in May, 1937, the left axilla being involved first followed a few days later by involvement of the right axilla. From thence it rapidly spread to the neck, chest, back, and posterior surfaces of the thighs. During a period of cool weather in June it subsided but was aggravated again with the onset of warm weather. The patient stated that she was troubled with excessive perspiration during the warm summer months. Examination revealed an acute, erythematous and

lar, weeping and crusted dermatitis involving the *axillae*, *anterior* *surface* *of* *the* *neck* *and* *chest*, *the* *upper* *part* *of* *the* *back*, *and* *the* *posterior* *surface* *of* *the* *thighs*. The lower border of the dermatitis was sharply demarcated by



Fig. 47.—Dermatitis due to a navy blue silk slip. Anterior view. Note the dermatitis limited to the area of contact with the upper part of the slip and its shoulder straps. (Netherton.)



Fig. 48.—Same case as shown in Fig. 47. The lower part of the buttocks and the thighs are areas of direct contact with the slip. (Netherton.)

the patient's brassiere and the upper border was roughly limited by the upper margin of her slip. It extended as narrow bands over the shoulders corresponding to shoulder straps (Figs. 47, 48). On the thighs, the upper margin of

the dermatitis was limited by the corset and the inferior margin by the hose. The nature and distribution of the dermatitis suggested the cause to be an article of the patient's clothing. She wore to the clinic the clothes that she had worn regularly throughout May and June. A patch test with her navy blue slip gave a positive reaction. Tests with material from her other clothing were negative. She stated that the slip had not been cleansed since she purchased it.

(B) THE PATCH TEST

The patch test has made possible much of the experimental and clinical investigation of the allergic nature of contact dermatitis and this work has given rise to certain criteria for the proper application, uses, and interpretation of the test. These are briefly described.

Technic.—Ordinary adhesive tape cut into squares about 2 inches on a side and squares of cellophane or rubberized silk

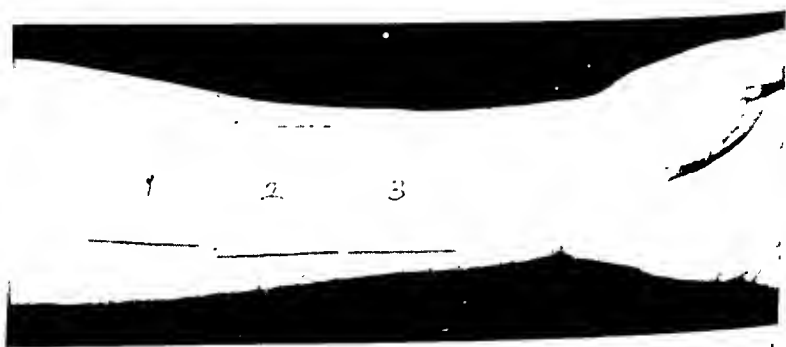


Fig. 49.—Patch tests on the forearm. This is the simplest method of patch testing. Biederman⁵⁰ has recently described a method by which many tests may be applied to a small area.

about 1 to 1½ inches on a side may be used. A small piece of the solid material such as cloth, leaf, flower, etc., or a small piece of old well-washed and clean sheeting or broadcloth is moistened with the liquid or ointment, etc., and placed next to the skin. When testing for powders and pollens, it is well to apply the substance with both a dry and moist portion. This is covered by the cellophane and the whole is covered by the adhesive plaster. The cellophane protects the skin around the substance from the irritating effects of the adhesive plaster, thus avoiding confusion as to which of the two produced the dermatitis. If volatile substances are to be tested in this man-

ner, the cellophane prevents the vapor from escaping through the adhesive plaster. The patch test usually is allowed to remain on the skin from twenty-four to forty-eight hours and is observed at the end of twenty-four, forty-eight, seventy-two, and ninety-six hours (Figs. 49, 50).

Volatile substances may be placed in a lipped test tube and the mouth of the tube strapped to the skin. It is left *in situ* for ten to fifteen minutes and then removed. With this



Fig. 50.—A positive patch test to the rotogravure section of a newspaper. Note the edema and vesiculation.

method, a control test *must be applied* to a normal skin at the same time. In neither method is the patient permitted to wash the test sites during the period of observation.

When hypersensitiveness to adhesive plaster is found,⁴⁶ the test may be applied by rimming the area with collodion which holds the cellophane as a cover.

Use and Interpretation.—The patch test is used to detect the *specificity* of the eczematous reactions but it is not

diagnostic. It is the *only* test applied to the skin known today which will aid in the identification of substances producing contact dermatitis. It should be remembered that the starting point lies in the history and either a positive or negative result should fit in with the information obtained in the history and not that obtained by a routine series of tests.⁴⁷ Each result, whether positive or negative, must be carefully checked by re-questioning the patient. In this respect, one must also bear in mind that in any large series of presumably normal people, from 0.2 to 65 per cent will be found to give a positive test to the long chain of sensitizing external irritants at one end of which are chemicals and at the other plants. Furthermore, the exact conditions of sunlight, heat, moisture, trauma, friction, infection, etc., under which the irritant acts cannot be duplicated by patch testing and can only be evaluated in retrospect, as indicated in the history (see the above case reports). False positive reactions may be obtained with concentrations of the substance stronger than those to which the patient has been exposed, if the time of application be too long, or if the irritant is applied to a localized area of hypersensitivity. The opposite conditions may give a negative result. Thus a positive test should be controlled under the same conditions by a negative result on a normal person. A false positive reaction occurs most frequently with the primary irritants. Tests with these should be applied beginning with the higher dilutions, 1 per cent to 10 per cent, and properly controlled. Other substances are diluted from one fourth to one third the concentration (liquids diluted with water or alcohol; ointments, etc., with petrolatum), to which the individual has been exposed.

Variability of the hypersensitivity of the skin influences the reaction so that one or a few tests do not permit positive conclusions, particularly if applied at the same time.⁴⁸ The test may result in a mild or no reaction or provoke a severe flare-up of the dermatitis.⁴⁹ Spontaneous desensitization may occur and the negative test may be due to the fact that it has been applied to an area no longer sensitive; on the other hand, there may be localized areas of hypersensitivity and tests applied at a distance may be negative as shown by Sulzberger and Kerr¹⁵ who demonstrated that in some cases of contact

dermatitis of the face and neck the patch test must be applied in the "V" area of the neck and chest. Therefore a single negative test with the substance strongly suspected in the history cannot be relied upon, and it must be tested several times in the proper areas. Whether or not a single test may be thought to be all that is necessary depends upon the strength of the evidence elicited by the history.

Polyvalent hypersensitivity in individuals is manifested by a positive reaction to several substances: thus a positive reaction to a single agent does not mean that the irritant producing the eczema has been found. In cases of long-standing eczema, the dermatitis may be persisting as the result of an added hypersensitivity to other substances long after the primary irritant has been removed from the individual's environment. The dermatitis may be aggravated by primary irritants which, if the epidermis were specifically hypersensitive to only one substance, would not affect the skin. Many tests with many different substances may be necessary before the eczema can properly be managed in view of the individual's environment.

Dermatologists habitually begin with low concentrations of the drugs used in external therapy and known to cause eczematous reactions. A negative patch test with the medicament permits its wide application in high concentration without danger of a severe dermatitis.

(C) DIAGNOSIS

The sudden onset of an acute erythematous, vesicular dermatitis with or without crusting which occurs at any time of the year and on any area of the cutaneous surface likely to come into contact with external irritants should arouse suspicion of contact dermatitis. The inflammation at first is usually limited to the area of contact and the history will almost always lead to the discovery of the irritating substance. Seasonal occurrence suggests plants as the cause. A positive patch test properly controlled is strong confirmatory evidence. Removal of the cause followed by subsidence of the dermatitis and recurrence of the dermatitis on reexposure establishes the diagnosis.

Seborrheic dermatitis differs from contact dermatitis by

absence of all of the criteria listed in Table 1. The greasy, yellowish crusting on irregular yellowish pink patches, dandruff, and predisposition to the seborrheic areas (scalp, ears, and behind the ears, sides of the nose, eyebrows, sternum, axillae, umbilicus, and midportions of the back) are important points. The *Pityrosporum ovale* is found in large numbers in the scales of the scalp and occasionally in the hairy regions of the chest, about the eyes and axillae.

In addition to the differences listed in Table 1, atopic dermatitis (disseminated neurodermatitis) occurs, as a rule, in patients under twenty years of age who usually have dry, thick skin with a tendency to grayish or brownish tinge and dermographia. The sites of predilection are face, neck, antecubital and popliteal spaces, and dorsa of the hands and wrists. Vesiculation is practically always absent unless secondary eczematization is present. These cases are very rarely seen early but present themselves with the above-mentioned areas as sites of thick, lichenified, excoriated, papular dermatitis. It is extremely rare to see this dermatitis in persons forty years of age and over. Sulzberger *et al.*⁴ have described this dermatosis and contrast it with contact dermatitis in great detail because the two are most frequently confused.

Lichen planus with its flat-topped, waxy, angular or polygonal pinpoint to pinhead sized papules which characteristically show white lines or points (Wickham's lines) and are often arranged along scratch marks should not offer much difficulty in diagnosis. Patches of the papules have a distinct violaceous color. The sites of predilection are the flexor surfaces of the wrists and forearms and the legs just above the ankles. Lichen planus is not due to allergy.

Lupus erythematosus of the face is usually extremely chronic and consists of well-defined, erythematous, scaling patches, often symmetrically distributed in the butterfly area of the face with raised borders, having tenacious scales which, when removed, will carry with them horny plugs from the dilated follicles. Usually on resolution, typical, superficial, stippled scars remain which are indelible and pathognomonic. Pruritus if present is slight, whereas in contact dermatitis itching is practically always present and prominent. In eczema the scales are superficial and do not involve the follicles.

Acute lupus erythematosus is among the more rare dermatoses. On the face, the erythematous patches blend and cover the cheeks, nose, eyelids, and ears. The face is edematous and swollen resembling erysipelas. The dorsa of the hands and fingers are involved and patches may occur on other areas. On the hands, the lesions may vary from erythema to purpura. The cutaneous lesions are usually accompanied by symptoms of toxemia, elevated temperature, arthralgia, and gastro-intestinal symptoms may be present. Leukopenia is characteristic and albuminuria is frequently noted. When the discoid variety becomes acute, the patches take on a markedly inflammatory aspect and they are accompanied by symptoms of toxemia, which practically never accompany contact dermatitis. Moisture is rarely present in lupus erythematosus while it occurs frequently in eczema.

Erysipelas is sometimes confused with contact dermatitis of the face. In erysipelas, the region across the nose and adjacent cheeks (butterfly area) is most frequently involved. The eruption is a streptococcic infection and usually progresses from a certain point, the skin is fiery red, while the borders are elevated, sharp and may show tongue-like projections. Outlying patches of erythema, papules, and vesicles are never present. It is usually accompanied by symptoms of toxemia. In contact dermatitis the eruption is diffuse, intensely pruritic, and the borders are irregular and indefinite with peripheral patches of erythema papules and vesicles with scratch marks. Symptoms of toxemia are rare unless a severe secondary infection ensues.

From contact dermatitis of the forearms, hands, and feet the following dermatoses are to be differentiated: dyshidrosis (pompholyx), dermatophytosis, dermatophytid, recalcitrant pustular eruption of the hands and feet, erosio interdigitalis blastomycetica, resistant vesicular dermatitis of palms and soles, infectious eczematoid dermatitis, brucella dermatitis, erysipeloid, nummular recurrent eczematoid dermatitis of Politzer. The morphologic differentiation of the dyshidrosiform eruptions from one another and from contact dermatitis is at times impossible and frequently every diagnostic aid must be utilized before arriving at a final opinion. Repeated and incessant questioning about possibilities of contacts, patch test-

ing with every irritant brought under suspicion in the history, repeated cultures and microscopic examinations for fungi, therapeutic tests, close observation as to the course and morphologic changes of the eruption are important for diagnosis. An attempt is made here to outline the distinguishing characteristics of the typical eruptions affecting the hands and feet as a starting point from which one may proceed in the separation of contact dermatitis from this group.

True dyshidrosis (pompholyx) is characterized by the sudden appearance of uniform, noninflammatory, deep-seated sago grainlike vesicles on various parts of the palms and soles. The subjective sensations are burning rather than itching; hence scratching and crusting are rare. The exfoliation following drying of the vesicles involves the whole epidermis and is similar to the exfoliation of scarlet fever. Many authorities believe this dermatosis to be a mycotic infection or dermatophytid eruption rather than a disorder of the sweat glands.

Dermatophytosis attacks any part of the hands and feet but the sites of predilection are the webs in the third and fourth interspaces between the toes. The vesicular and squamous types are sometimes confused with contact dermatitis. The mycotic vesicles are deep or superficial, mildly inflammatory, spread peripherally forming circinate or gyrate, sharply defined vesicular margins. Various stages of development of the patches of vesiculation are seen. When the vesicles dry up, the scales form a collarette or brown hyperkeratotic buttons, especially on the palms and soles. In early or untreated cases, fungi are found on culture or microscopic examination of the scales and vesicle roofs. Often dermatophytosis is eczematized by treatment; or a contact dermatitis is superimposed on the original fungus infection.¹⁵ Dermatophytosis of the hands is uncommon, but should always be ruled out.

Dermatophytids usually affect the palms and the dorsum of the distal halves of the fingers and their margins. The eruption may be dyshidrosiform (see dyshidrosis) or squamous. It is rarely inflammatory unless secondary pyogenic infection supervenes. Frequently, but not always, dermatophytosis of the feet is found. Usually the "id" eruption disappears when the accompanying dermatophytosis of the feet is cleared up. Desensitization with fungus extracts sometimes is of value in

the diagnosis. Rarely does the "id" eruption become generalized. Table 1 lists the typical differences between contact dermatitis and epidermophytosis and "ids."

Pollitzer described a dermatosis affecting a number of individuals who exhibit coin-shaped and sharply defined patches of vesicular dermatitis favoring the dorsum of the hands and forearms. The patches attain full development almost at once and pursue a protracted course, lasting for weeks or months or they may be recurrent. The patches are uncommon on the dorsum of the fingers. Itching is variable. The lesions may become eczematized by treatment. The etiology is unknown and no history of contact can be obtained.

From the above dermatoses, contact dermatitis is differentiated by a history of contact in the latter and confirmation of these leads by the patch test. Morphologically, typical acute contact dermatitis is diffuse with ill-defined borders, acute inflammation, and *superficial* vesiculation of the epidermis. Later, there is infiltration of the skin and the scaling is superficial with the scales firmly attached to the infiltrated base. The sites of predilection are the dorsum of the forearms, hands, fingers, webs between the fingers, and dorsum and sides of the feet and ankles, the areas of dermatitis being limited to areas of contact. The dermatitis does not recur unless there is reexposure.

Erosio interdigitalis blastomycetica occurs on the webs of the fingers especially of persons who frequently have their hands in water for long periods. It is a yeast infection and is characterized by a red, shiny dermatitis of the webs surrounded by a collarette of scales; or the epidermis may be thick, white, and sodden. Culture of the organism assures the diagnosis. Contact dermatitis of the webs of the fingers always is accompanied by lesions elsewhere on the hands.

The lesions of infectious eczematoid dermatitis begin from a starting point of infection and extend peripherally and with well-defined vesicular borders often undermined. The vesicles are larger than those of contact dermatitis. The regional lymph glands are usually involved in the process. It is auto-inoculable and staphylococci or streptococci are obtained on culture.

Erysipeloid is characterized by an erythema which spreads

peripherally on the fingers and hands and, with clearing in the center, forms circinate patterns. The lesions are violaceous or purple red and do not itch or form vesicles such as are seen in contact dermatitis.

The dermatitis of the hands and feet in the milder forms of the cutaneous manifestations of pellagra may at first be confused with contact dermatitis, but the history of geographic occurrence, stomatitis, gastro-intestinal and mental symptoms in addition to the symmetry of the dermatitis and involvement of face and neck and the course of the disease readily distinguishes the former.

Recalcitrant pustular eruption of the palms and soles are limited to these areas. The lesions are deep-seated pustules filled with sterile exudate. Itching is prominent when the pustules are erupting. The dermatosis does not spread by extension but by new pustules at a short distance from the earlier ones. The toes and webs are never attacked, but the lesions have appeared on the palmar surface of the fingers. As the pustules dry up, there is scaling. There is no history of contact with external agents and, when contact eczema involves the palms or soles and becomes secondarily infected, pyogenic organisms are present.

Localized neurodermatitis on the dorsa of the feet and about the ankles should offer no difficulty in diagnosis unless there is secondary eczematization due to treatment. The lichenified patch of coalescing papules with increased skin markings and paroxysmal itching, which has been present for months or years, without receding, readily distinguishes the disease from contact dermatitis. Frequently, other lesions on the extensor surfaces of the forearms near the elbows, tibiae, and nape of the neck are associated.

An eczematoid dermatitis that occurs on the dorsa of the feet about the ankles, and on the legs in persons who suffer from varicose veins and other circulatory disturbances should not be confused with eczema. The presence of varicose veins, pigmentation, brawny edema, and scars of previous ulcers serve to distinguish the former. Evidence of circulatory failure due to cardiovascular disease, *i. e.*, dependent edema and other signs of chronic passive congestion, is against a diagnosis of contact dermatitis.

Brucella dermatitis is a rare disease usually affecting the forearms of those who milk infected cattle. In mild cases there may be an erythema and pruritus of a few days' duration while in the more severe type the eruption is papular and papulopustular. The disease is self-limited but may recur on exposure.

TREATMENT

The treatment of contact dermatitis may be divided into three parts: first, and most important, the external irritant or irritants must be identified and removed from further possible contact with the patients or the patient from his environment if this is possible. Second, during the search for the offending substance and after its removal, soothing, local applications are indicated. Third, desensitization may be tried in the dermatitis due to plants, housedust, etc.

The first principle needs no further explanation.

In the acute moist stages, therapy is directed toward reducing the edema, drying up the vesiculation, relieving the pruritus, and preventing a secondary pyoderma. For this purpose we use cold aluminum acetate solution, 1:120 to 1:60, as wet packs followed by a lotion containing zinc carbonate 20 Gm., zinc oxide 20 Gm., glycerin 5 Gm., aqua calcis 120 Gm., aqua rosae q.s. ad 240 Gm. to which 1 per cent phenol is added. The larger vesicles and bullae should be opened and drained. After the acute symptoms have subsided, equal parts of the above lotion and olive oil applied to the affected areas prevents excessive drying and a sensation of "drawing" or "pulling" of the skin. Ichthyol, 5 to 10 per cent, or liquor carbonis detergens, 3 to 5 per cent, added to the lotion exerts a beneficial keratoplastic effect. Secondary pyoderma is quickly cleared up with potassium permanganate solution 1:5000 to 1:2000.

The infiltrated, lichenified and scaling dermatitis may be reduced by various ointments containing tar. For this we have found the following ointment of distinct value:

	Gm.
R Ung. Pix Liquida	4.0
Zinci Oxidi	4.0
Amylum	10.0
Ung. Diachylon	4.0
Petrolatum alba	q.s. ad 30.0

Ormsby¹⁸ states that sodium thiosulfate given intravenously in doses of 0.5 Gm. the first day and 1 Gm. on the second, third, fifth, and seventh days shortens to a week or ten days the course of cases that would extend over a period of weeks.

All stages of contact dermatitis with or without secondary pyoderma yield readily to superficial roentgen therapy. In our hands, unfiltered roentgen rays in doses of one fourth skin erythema dose at weekly intervals materially shortens the course and quickly aids in the amelioration of symptoms. The combination of tar ointments and roentgen rays gives the best results in reducing the thick skin which has been present for years.

Intensive studies in desensitization of individuals to the plants and other allergens have shown that, in the successful attempts, a state of relative hypersensitivity continues to exist, *i. e.*, a state of hyposensitivity. This is explained by Sulzberger²² and others as due to a relative lowering of the degree of hypersensitivity brought about by injections of the oil extracts of the plants. This lowering of sensitivity may be sufficient to prevent dermatitis under conditions in which the natural exposure is moderate or slight; but not sufficient to prevent clinical recurrence under massive exposure. It is a well known fact that, after a course of either curative or preventive injections of the plant extracts, patch tests with the extracts give positive reactions. This is comparable to massive exposure.

Both prophylactic and hyposensitization treatment is best given by intramuscular injections of the plant extracts in oil,* 0.5 cc. of 1 per cent extract being given once or twice weekly in the deltoid or gluteal muscles for 3 or 4 injections. Care should be taken to prevent the extract from coming into contact with the epidermis.

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* These extracts are supplied by Lederle in syringes with sterile needles ready for use.

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DIAGNOSIS OF DYSPEPSIA OF EXTRAGASTRO- INTESTINAL ORIGIN

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IN the presence of disease, unpleasant sensations arise sooner or later to apprise the host of the unfriendly intruder. These warnings, which we call symptoms, and the pathologic changes in the structure and functions of the body, which we call signs, are the clues on which we must rely if the nature and location of the underlying disease process is to be discovered.

Due to the highly complex and closely integrated functions of various parts of the body and to the intimate relationship of the nervous system and the vascular tree to all parts of the body, the symptoms of disease not infrequently disturb some domain other than that where the disease is located. The disease may be of a general systemic nature, affecting the functions of the body as a whole, but the predominant symptoms may be strictly localized in one organ or system of organs. The nerve supply to the site of the disease may intercommunicate so closely with other organs that the symptoms are shunted from the diseased to a nondiseased site.

The digestive system is an especially sensitive indicator of the presence of disease, and the functions of the gastro-intestinal tract are extremely prone to be disturbed by distant local disease or general systemic disease. This may occur long before other localizing symptoms make their appearance. In many diseases that are accompanied by digestive symptoms, there are definite signs and symptoms that clearly point out the disease site. In other diseases, however, the symptoms are so predominantly referred to the gastro-intestinal tract and other signs are so obscure that attention is directed away from the true lesion. It is in such cases that exceptional acumen is necessary to prevent our being led astray in efforts to localize and diagnose the real source of the symptoms.

Unfortunately, we are confronted by two very large diagnostic pitfalls when we approach a patient whose symptoms are chiefly referable to the gastro-intestinal tract. These pitfalls are so gaping that I do not believe it is possible for anyone to prevent falling into them occasionally, but our chance of crossing them safely increases immeasurably with the skill with which we select and use our diagnostic aids.

In our diagnostic attempts to find the cause of gastro-intestinal symptoms, we seem to pick and choose our way very carefully up to that point where the available methods of examination fail to reveal any disease of the gastro-intestinal tract that will satisfactorily explain the symptoms. At this point, we are on the slippery banks of the first pitfall. Will we slide into it and ascribe the symptoms to a functional disturbance?

Functional indigestion is by far the most frequent cause of digestive symptoms so that if, in the absence of discoverable disease, the symptoms strongly suggest functional disturbance, the chances that it is functional are so great that we readily slip into this diagnosis and there is an excellent possibility that it will be correct. Occasionally, however, we err and the purpose of this discussion is to show ways and means of preventing ourselves from slipping into this error and to suggest methods for retrieving the mistake in case it is made.

If we hurdle this pitfall in full stride and decide that only definite pathology can explain the symptoms, we immediately arrive at the second pitfall. This is the error of assuming that the cause of digestive symptoms must arise in the gastro-intestinal tract and that an exploratory operation is necessary to determine the causative lesion. This is true in a sufficiently large number of cases that the possibility of its being correct is also very good. However, we have all seen mistakes of this kind with occasional disastrous results to the patient.

If we are medically minded, we very seldom cross the first pitfall to reach the second, but if we are surgically minded we often detour around the first and don't even know it is there.

Can we safely get across these two pitfalls in those cases where gastro-intestinal symptoms are not the result of primary functional and organic disease of the gastro-intestinal tract? In many cases I believe we can and I will endeavor to point out

some of the very common causes of such gastro-intestinal symptoms and certain diagnostic clues that lead us to them.

I might proceed and enumerate a number of diseases that fall into the group under discussion and describe the gastro-intestinal symptoms that usually arise from these diseases. Since such symptoms are practically always the same as some functional or organic condition, this method of approach would put us on the other side of the hurdles without showing the way across.

Good diagnosis is a combination of art, knowledge of disease processes, and keen powers of observation. In addition, the mental processes must follow some orderly methods of progressing toward the final conclusion. In the cases under discussion, the diagnosis must be reached by methodical progression away from the gastro-intestinal tract.

I want to emphasize here that extragastro-intestinal pathology as the cause of dominant gastro-intestinal symptoms is greatly in the minority and must only be thought of and sought after primary gastro-intestinal disease has been eliminated as far as is possible with our diagnostic methods.

It should be emphasized that the discovery of a lesion elsewhere that could satisfactorily explain the gastro-intestinal symptoms should not eliminate the necessity for ruling out primary gastro-intestinal lesions that can just as well be a cause of the symptoms. It is therefore right and proper to approach all patients presenting gastro-intestinal symptoms as if the symptoms were of gastro-intestinal origin.

Routine methods of history taking, examinations, roentgen examinations, and laboratory studies will give a satisfactory explanation of the symptoms in a high percentage of cases. In others, where the diagnosis is still not definitely established and where we feel positive, from the nature of the symptoms, that they could arise only from definite gastro-intestinal pathology, appropriate measures, such as exploration, are undertaken for relief and confirmation of the diagnosis. Some cases are distinctly of a functional nature so that little concern need be felt about the accuracy of this diagnosis.

A fair percentage of cases, however, do not fall into these easily classified groups. Some features of the problems will be puzzling and difficult to explain on a basis of functional dis-

orders. The evidence of a pathologic process in the gastro-intestinal tract will be extremely vague and indefinite. In other words, when the diagnosis is not completely evident and you are slightly puzzled, pause for a moment, review the evidence, prepare for a fresh approach to the case before jumping or falling into one or the other of the two great pitfalls. Without suspicion, without doubt of the correctness of any diagnosis made on insufficient evidence, there is little hope that one can be sufficiently on the alert to detect those occasional cases that make the practice of medicine a pleasure and a stimulation.

We have now reached the point in this discussion where we come to that small percentage of patients who present, in the main, gastro-intestinal symptoms, who have been thoroughly studied in the manner that gastro-intestinal problems are usually studied, and in whom no definite explanation of their symptoms has been found. We will assume that some discrepancy of symptoms or signs makes the physician hesitate, at least a little, to make a diagnosis of either functional indigestion or indefinite gastro-intestinal disease.

We might inquire here, what is it about these cases that causes this hesitation on the part of the physician?

It is something that is difficult to set down in words, something that comes to the physician with increasing experience, something that is told by the patient's manner, his personality, and by the careful analysis of his symptoms in relation to his whole being. The patient may have a fairly definite type of distress that does not appear to be due to functional causes and it is not characteristic of gastro-intestinal disease or, if so, this disease has been satisfactorily eliminated. His symptoms may definitely indicate a functional disorder but his personality may not be compatible with this diagnosis; the onset of a functional type of distress after many years of good health would be incompatible with the proposed diagnosis; in spite of a functional type of symptoms the patient may appear to be ill; the location or type of pain may be sufficiently unusual to arouse doubt; some previous treatment or operation may have failed to relieve the symptoms which it should have done if the disease were of gastro-intestinal origin; or the age or something else about the patient may not be in accord with func-

tional or organic gastro-intestinal disease. These and many other discrepancies serve to give us an impression that we are dealing with disease that is not functional and probably not organic gastro-intestinal disease, but is still unexplained.

It would be very helpful if we had some way of determining whether some extragastro-intestinal lesion actually existed as the cause of symptoms. Positive evidence of the presence of such a lesion would spur our search until it was located. With nothing more than suspicion as evidence on which to base a search for something that may not exist and which may cost a great deal of time and money, we are psychologically handicapped from the very start. To overcome this handicap, we must formulate some method of conducting our search that will lead us to the most likely sources of trouble with the least possible effort.

As mentioned previously, the first requisite to finding such a lesion is to suspect its presence. The search should be started by carefully questioning the patient in order to elicit minor symptoms of disturbances in other locations, as in the urinary tract, the cardiovascular system, the pulmonary and nervous systems, for these might previously have been overlooked or regarded as insignificant. The slightest evidence of abnormality should be viewed with suspicion. If any good clues are brought out by this review of the history, they should be investigated by a more detailed clinical examination and the necessary special examinations should be carried out. These clues may prove fruitless or, in many cases, no such clues will be found.

In such cases the next step is to make certain examinations in the order of the specificity of gaining exact positive and negative information and also the frequency with which the examined domains cause gastro-intestinal symptoms.

Let us now review certain common causes of gastro-intestinal symptoms. Disease in the urinary tract is a very frequent source of gastro-intestinal symptoms. In many cases, there are no associated genito-urinary symptoms. Such lesions most frequently cause indefinite but fairly well localized pain in the flanks or upper or lower quadrants of the abdomen. They also produce motor and secretory disturbances and reproduce all the symptoms of functional indigestion. Lesions

in the kidney have led to many useless exploratory operations. In our series of cases, 33 per cent of the patients who have had gastro-intestinal symptoms due to lesions in the urinary tract had previously had the removal of some pelvic or abdominal organ without relief from symptoms. These lesions are most frequently obstructive lesions (hydronephrosis) or irritating lesions (stones). Infections and tumors occasionally cause symptoms.

A study of the urinary tract in indefinite gastro-intestinal symptoms will yield a surprisingly high percentage of positive findings and should never be omitted. Because methods of study of the urinary tract are so accurate in giving definite, positive and negative evidence, this should be one of the first sources of gastro-intestinal symptoms to be ruled out.

Examination of the urine frequently gives a helpful clue, especially when pus, blood or albumin is found, but on other occasions the urine may be entirely normal. It is our custom to have a film of the kidneys, ureters, and bladder made in connection with our roentgen study of the gastro-intestinal tract. This is helpful in showing the size, shape, and position of the kidneys. Unsuspected kidney and ureteral stones will be found in this way. The cases of obstruction require further study. An intravenous urogram will usually suffice or at least give some evidence that further study, such as retrograde pyelography, is required. In this manner, we have been able to detect many early hydronephrotic lesions and thus institute treatment to remove the cause of the obstruction and save the kidney. Too frequently such patients have been treated for gastro-intestinal symptoms for years, only to have the real cause of the trouble discovered when a shell of the kidney remained.

Allergy is probably the most frequent cause of gastro-intestinal symptoms in the group of cases under discussion. This subject has been thoroughly reviewed elsewhere in this clinic and requires little discussion here. Unfortunately, the methods of study of allergy do not conclusively prove that the symptoms are due to this cause, and doubt as to the etiology should persist until management of allergy has given therapeutic proof of its causal relationship. Because of this fact, investigation of allergy is suggested after study of the urinary

tract, even though allergy is a more frequent offender. The allergist has certainly been a great help to the gastro-enterologist in solving many of his problems of chronic disease.

Incipient tuberculosis often gives its first warning through gastro-intestinal symptoms. This is especially true in the young adolescent of the asthenic type. These cases, of course, do not go undiagnosed for very long because the real trouble soon becomes evident. If, however, the significance of the first warnings of tuberculosis are not recognized, we often lose that advantage of time which marks the difference between success and failure in the treatment of tuberculosis. The roentgen examination of the chest offers such conclusive evidence that it should never be omitted in cases of unsolved gastro-intestinal symptoms, and this is especially true in patients in the age group from ten to thirty-five years.

Gastro-intestinal manifestations of cardiovascular disease are extremely common. In many cases, the recognition of this fact is so apparent from the history and physical examination that only a small percentage of cases remain to be included in the group I am discussing. When the signs of congestive heart failure are present, gastro-intestinal symptoms are rarely absent. Often, however, before true signs of congestive failure become apparent, the patient will complain of digestive symptoms. Anorexia, postprandial distention, and mild nausea in the middle-aged and elderly individuals should call for a complete cardiovascular study. In many cases, the source of the earliest symptoms is difficult to trace other than by a therapeutic test with rest and small doses of digitalis, but suspicion should arise where the symptoms are related to the size of the meal and to exertion shortly after a meal.

The more spectacular symptoms of attacks of vomiting and severe epigastric pain due to disease of the coronary arteries may be easily confused with pathology in the gastro-intestinal tract. The best way to avoid these mistakes is to take a careful clinical history from a cardiovascular viewpoint rather than a gastro-intestinal one. In practically all cases, the deciding clue will be found in the history. Finally, of course, the electrocardiogram is a most helpful diagnostic aid. In general, it may be said that, while the gastro-intestinal manifestations of cardiovascular disease occur with great frequency,

it is usually not a difficult problem to trace the source of these symptoms because of the definitely associated cardiovascular symptoms in most cases. On occasion, however, it becomes confusing and must be given careful consideration in some of the unexplained gastro-intestinal problems.

Lesions located in the central nervous system frequently produce gastro-intestinal symptoms which, at times, may be quite confusing in making a differential diagnosis.

Vomiting is the cue symptom to lesions located in the central nervous system and may or may not be of the projectile type. It is one of the cardinal symptoms of increased intracranial pressure and may appear as one of the earliest symptoms of pressure. Here again the importance of early recognition of the causative lesion lies chiefly in preventing the irreparable damage that a short period of delay will often produce in the patient's vision. Such cases appear just infrequently enough to catch us off guard. To prevent the chagrin that always goes with permitting a high degree of choked disk to develop while we are treating a supposed gastro-intestinal disorder, one should cultivate an automatic reflex to think of increased intracranial pressure in all cases of vomiting without other specific cause. Study of the fundus and spinal puncture should be early and not late examinations in such cases.

The gastric crises of tabes with girdle pains and vomiting simulate disease of the gallbladder and peptic ulcer. Not infrequently, one or the other of these lesions will also be found in the patient who has tabes dorsalis. There is a distinct tendency, however, to omit a roentgen examination of the gastro-intestinal tract where the clinical signs of tabes are so evident and to be satisfied that the symptoms are due to syphilis. Such a course frequently leads to error, as the symptoms may be due to true gastro-intestinal disease and will only respond to appropriate treatment of the gastro-intestinal lesion.

The root pains due to disease of the spinal cord are most difficult to evaluate when they occur in the segments of the abdominal area. The real lesion is rarely discovered until other neurologic signs appear. Less prejudice against the harmless procedure of a spinal puncture would reveal these lesions much earlier.

Two other lesions which are intimately connected with the

central nervous system are often curiously mistaken for gastro-intestinal disease. I refer to migraine headaches and labyrinthine disturbances. Both of these conditions have such characteristic prodromal symptoms preceding the nausea and vomiting that the history usually suffices to make the diagnosis clear. Headache or dizziness preceding nausea and vomiting should direct the attention away from the gastro-intestinal tract.

The nausea and at times the vomiting, especially in children, that accompany errors of refraction and muscle balance of the eyes may be very deceiving. There are no definite clues to the real cause and it is found only by prescribing a study of refraction. In children with periodic nausea and vomiting, two studies, investigation of allergy and refraction of the eyes, should never be omitted.

Focal infection and walled-off pyogenic infection are extremely common causes of reflex digestive disturbances. I have not mentioned this in the proper sequence of frequency because a routine physical examination should seek to discover the usual sources of focal infection and their discovery implies removal. Walled-off pyogenic infections usually cause sufficient constitutional and local symptoms to warn one of their presence and to lead to their discovery.

Pelvic disease will be omitted from this discussion because it is so intimately associated in the mind of every physician with true gastro-intestinal disease that it is always a part of the routine study of the gastro-intestinal tract.

The gastro-intestinal symptoms caused by heavy metal poisoning is due to true gastro-intestinal irritation from the excretion of the metal by the colon. The clues to the correct diagnosis, however, appear elsewhere and require that this possibility be kept in mind if the appropriate examinations are to be made to detect the signs of this condition. All occupational exposure to lead should be properly checked but, occasionally, an unusual source of lead exposure will create a puzzling diagnostic problem.

Diseases of the lower dorsal and lumbar spine may present confusing problems in the differential diagnosis from gastro-intestinal disease. This is especially true of the hypertrophic or degenerative types of arthritis of the spine. These chiefly

manifest themselves as radicular pain that is confused with pain of the intra-abdominal organs or peritoneum. At times, the pain is more generalized. The age of the patient, the presence of definite symptoms of arthritis elsewhere in the body, the relation of the pain to rest, exercise, and posture, and the elimination of other diseases are helpful aids in differential diagnosis. The most helpful diagnostic point is to try to distinguish between superficial skin sensitivity and deep tenderness, the patient himself rarely being able to do this by the subjective sensation he experiences.

One can think of many other conditions that have caused confusion with gastro-intestinal disease. The vastness of this subject makes a discussion of all possible extraneous causes of gastro-intestinal symptoms an impossibility. I have attempted to show in which direction the physician's mind should wander in those cases in which he has not found an adequate explanation for the symptoms and during the course of the wandering I have suggested, he will almost surely find clues that will also detect those atypical and less frequent causes of gastro-intestinal symptoms that have not been considered here.

I have tried to discuss this subject in a way that will not overemphasize the frequency of the lesion under discussion and in a way that will not prematurely direct the examiner's attention away from the gastro-intestinal tract. There comes a time, however, in certain patients presenting gastro-intestinal symptoms, when one's attention must be directed elsewhere if the etiologic factor is to be determined.

I want to warn that one must not be discouraged by the large number of negative examinations that are required to detect a relatively small number of lesions of this kind, but until such lesions are found, the patient will continue to suffer and in many cases progress to the point where recovery is impossible or the treatment is all out of proportion to what would have been necessary had the lesion been discovered in an early stage.

I would also like to warn that I believe it inevitable that cases of this kind will always be misdiagnosed and undiagnosed but the percentage will become smaller as we stop, look, and listen before we blithely make a diagnosis of functional indigestion or explore the body before exploring the abdomen.

CHRONIC DYSPEPSIA: COMMON CAUSES AND APPROACH TO TREATMENT

E. N. COLLINS

THE definition of chronic dyspepsia varies according to individual interpretation. If it applies to disturbance in gastric function and if the stomach is considered the "alarm box" of the abdomen, it obviously applies to numerous organic, reflex, systemic, and functional causes. However, the purpose of this discussion is to consider only the commonly encountered causes of chronic dyspepsia and to emphasize the methods of examination and approach to treatment which have proved most significant in our experience.

It is axiomatic that effective treatment is largely a matter of accurate diagnosis. To attain this it is established that a *detailed history*, painstakingly obtained and interpreted by an experienced observer who is primarily interested in gastrointestinal dysfunction, and *reliable roentgen examinations* are of first importance. The physical examination may yield no evidence of abnormality. Another valuable procedure, when possible, is a period of observation of the patient in the hospital, where numerous functional tests and examinations of the stools can be made, as well as observation of the response of the patient to treatment.

METHODS OF EXAMINATION

When the history is characteristic of well-known syndromes, the diagnosis and type of treatment indicated are usually simple. Nevertheless, before treatment is instituted, certain laboratory procedures should be made. There are many causes for gastric symptoms and it is known that an ulcer on the posterior wall of the duodenum may produce symptoms highly suggestive of biliary disease, and symptoms highly suggestive of peptic ulcer or gastric neoplasm may be due to biliary disease or abnormality in other adjacent organs. Be-

cause of these facts, during the past fifteen years, we have done and will continue to routinely include a roentgen examination of the stomach whenever there is a request for cholecystography, and include cholecystography whenever there is a request for roentgen examination of the stomach.

The Roentgen Examination.—Many of the patients whom we encounter do not present distinctive histories. Diagnosis obviously involves a process of exclusion. The type of roentgen investigation made in these instances has been published.¹ Routine films of the chest and urinary tract are made first. Abnormalities in the chest causing reflex gastric symptoms are occasionally encountered. These may not have been apparent from the history and physical examination. The absence of significant physical findings in the presence of early tuberculosis and metastatic lesions in the chest is well known.

Many patients without urinary symptoms or abnormal findings on urinalysis have primary disease in the urinary tract which cause reflex symptoms in the gastro-intestinal tract. When plain films reveal abnormality in the urinary tract, the patient is sent to the genito-urinary department for further investigation. Intravenous urography or retrograde pyelography may be indicated. Thus, the treatment of chronic dyspepsia may involve treatment of an abnormality in the urinary tract.

If a roentgen gastro-intestinal series' examination is indicated, films of the gallbladder area as well as those of the urinary tract are made the first day. That night, the cholecystographic dye is taken. The next day, as soon as the cholecystograms are satisfactory, the barium meal examination of the stomach² is made, and the following morning the barium enema examination of the colon³ is made. Thus, comprehensive roentgen examinations, including the "double-dose cholecystographic procedures," need require no more than three days.

ORGANIC CAUSES OF DYSPEPSIA

CLINICAL ASPECTS

Although at least half of the patients seen by an internist primarily interested in diseases of the gastro-intestinal tract are found to have functional disorders, the latter diagnosis, of

course, should not be made until organic, reflex, and systemic causes for the dyspepsia have been excluded. In our experience, the most common *organic* causes of gastric symptoms, in the order of frequency, are biliary disease, duodenal ulcer, carcinoma of the stomach, and benign gastric ulcer. This experience coincides with that of Eusterman and Balfour,⁴ Dwyer and Blackford,⁵ and others.

DUODENAL ULCER

Of the *intrinsic organic causes* of chronic dyspepsia in the stomach and duodenum, duodenal ulcer has first rank. A deformed duodenal bulb, as revealed by roentgen examination, in the absence of visualization of an active ulcer crater (the niche), does not by itself mean that the cause of the present chronic dyspepsia has been found. Once the duodenal bulb becomes deformed, due to an ulcer, it may remain deformed throughout the remainder of that individual's life. In other words, a deformed bulb may signify that an active ulcer has been present sometime in the past and has been healed for many years, or it may signify that an active ulcer is present at the time of the roentgen examination. If the finding is associated with a history characteristic of the well-known ulcer or hyperacidity syndrome at the time of the examination, if gastric aspirations reveal a high free acidity, if roentgen examinations of adjacent organs reveal normal findings, and if taking a glassful of milk gives complete temporary relief of the symptoms, the objective roentgen finding mentioned assumes considerable importance. Otherwise, the roentgen examination of adjacent organs may be of greater importance from the standpoint of objective evidence. On the other hand, when a reliable roentgen examination, including careful examination by use of the fluoroscope, reveals the presence of a niche—the visualized ulcer crater—an active ulcer may be said to be present, regardless of the symptoms.

The *relief of symptoms* in the case of active, uncomplicated duodenal ulcer is the simplest problem with which the gastroenterologist has to deal, far simpler than dealing with functional disorders. In fact, the symptoms are relieved so quickly that the patient often does not follow the prescribed management long enough to permit healing of the ulcer. Although he

has been warned to the contrary, he believes his ulcer is cured when the symptoms have been relieved. Some time later, particularly if complications supervene, a surgeon may say, "After nine so-called medical cures of the ulcer, we will now operate."

The type of treatment indicated for active duodenal ulcer will, of course, depend upon the presence or absence of complications. A patient who has chronic dyspepsia due to duodenal ulcer may suddenly have an acute perforation or a massive hemorrhage, although either complication may occur without previous symptoms of ulcer. These complications are emergency problems and the details of management are beyond the scope of this presentation.

The third complication of duodenal ulcer which requires unusually careful management is that of obstruction. It is well recognized that, when the obstruction is due to *cicatricial stenosis*, we have the ideal indication for surgery. Gastro-enterostomy alone is curative. However, the conclusion that the obstruction is due to actual fibrosis must be based on the response of the individual patient to medical management.

When *symptoms of obstruction* have been present for long periods of time or where there is a history of recurring symptoms of obstruction, definite cicatricial stenosis at the pylorus is usually present. In these instances, there is generally atrophy of the secreting gastric glands which results in low acidity, and surgery should not be unduly delayed. However, when symptoms of obstruction come on abruptly and have been present only a short time, particularly in younger individuals, even though the roentgen examination shows a complete gastric retention in six hours, the obstruction may be relieved within a week or two by medical management. In these instances, there is usually a gastric hypersecretion and a high free acidity, and the obstruction is due to spasm or inflammatory edema. If careful medical management is continued over a sufficient period of time, the obstruction may never recur. It should be remembered that, if surgical procedures are used, gastro-enterostomy alone may be attended with poor results in these cases. Partial gastrectomy and partial duodenectomy, using the Billroth I or II procedures, when possible, seems to be the operation of choice at the present time.

All patients with symptoms and findings of obstruction should have hospital management. In addition to the need for daily gastric lavage and strict management of the ulcer, the patient is usually dehydrated and presents symptoms of alkalosis. Many details need to be considered in these instances, regardless of the degree of obstruction. Although marked pyloric obstruction would not ordinarily be discussed under the heading of "chronic dyspepsia," some of the details of management, such as *fluid therapy*, we believe, need emphasis. Initial urinalysis often shows a high specific gravity; there is diminished urinary output, and there is a marked diminution in urinary chlorides. The importance of making a determination of the urinary chlorides cannot be overemphasized because these patients usually need large amounts of chloride. A simple determination of urinary chloride which can be done by a nurse is one described by Fantus.⁶ Ten drops of urine are placed in a test tube and 1 drop of 1 to 5 potassium chromate is added. The color of the urine is now a canary yellow. Then, using the same dropper, add drop by drop a 2.9 per cent solution of silver nitrate while shaking, until the color changes to a brick red (silver chromate). The number of drops required to produce the change in color expresses in grams the content of chloride per liter of urine. When normal chloride balance is present, the urine contains at least 0.5 per cent of chloride, or 5 to 10 Gm. of chloride in the twenty-four-hour specimen. Before undertaking surgical procedures in cases of pyloric obstruction, the urinary output during the previous twenty-four hours should be at least 1500 cc., and this urine should contain at least 5 Gm. of chloride. The healing of the tissues alone, to say nothing of the smoother convalescence in general, warrants this minimal requirement.

The marked alteration in the metabolism of the body tissues has recently been summarized by Haden.⁷ The blood urea, nonprotein nitrogen, and carbon dioxide combining power of the plasma are elevated and the blood chlorides are diminished. In order to determine the chemical state of the patient, the following determinations are advised: urea or nonprotein nitrogen of the whole blood, chloride content of the plasma, carbon dioxide combining power of the plasma, total serum

protein in the blood, as well as total chloride and total non-protein nitrogen in the urine.

In the *treatment of the toxemia* due to pyloric obstruction, aside from the administration of fluids parenterally to overcome dehydration, surprisingly large amounts of sodium chloride are often needed to establish normal chloride balance. As Haden has mentioned, if the toxemia is well developed, about 1 Gm. of sodium chloride per kilogram of body weight is often necessary, which means that 70 Gm. are needed for an average man of 154 pounds. We commonly give a solution of 3 per cent sodium chloride in 5 per cent glucose intravenously, very slowly, and 3 per cent glucose in normal saline solution subcutaneously, until the level of the chlorides of the blood and urine are normal, but higher concentrations have been used with safety. If unusual dehydration is present additional normal saline solution may be given in the form of retention enemas. The hypertonic saline solution is usually given in amounts of 500 cc. every six to eight hours, the only contraindications being renal or cardiac failure, which may prevent the excretion of salt and water.

In cases of marked inanition, where the administration of additional glucose solution intravenously is indicated in order to raise the glycogen reserve, we believe the addition of insulin is advisable. Urinalyses during or soon after the administration of 10 per cent (or higher) concentrations of glucose will show the presence of sugar unless the glucose solution has been administered very slowly. It must be remembered that, if sugar is found in the urine during or soon after glucose administration, the patient is being partially dehydrated, for every gram of sugar that spills over in the urine carries 20 or more cubic centimeters of fluid with it. In the average non-diabetic patient, no more than 50 Gm. of glucose per hour can be fully metabolized, unless the glucose is combined with insulin.

The retention diet* used in cases of *pyloric obstruction* consists of two hourly feedings of foods which pass through the pylorus most easily, the remains of which are most easily aspirated through the stomach tube. Milk and cream are not

* Strained cereals, plain malted milk. plain ice cream, egg nog, gelatins. Junket, etc.

given until and if the daily gastric aspirations show a marked reduction in amount. The colloidal suspension of aluminum hydroxide is used between feedings every two hours. It is amphoteric, produces no secondary rise in secretion of hydrochloric acid, and does not lead to alkalosis or change in the values of the blood pH . Doses of 2 teaspoonfuls are given after the nightly aspiration and, in cases of continued secretion (determined by midnight and morning fasting aspirations), the patient is awakened and given the same amount every two hours during the night. Mineral oil and granulated agar are often needed to prevent hard stools until the patient is on a well-balanced diet.

When the patient is given the treatment outlined, it is surprising how quickly obstruction due to duodenal ulcer is relieved, when it is the result of spasm or inflammatory edema. Even though the initial roentgen examination revealed 100 per cent retention in six hours, it is not unusual for the obstruction to be relieved in a few days. The decision as to the indication for surgery has been made in a shorter period of time than was the custom while using the older well-established procedures, and the preparation of the patient for operation when proved cicatricial stenosis is present, has consumed less time.

No surgeon likes to operate when there is marked dilatation of the stomach. The stoma of a gastro-enterostomy may close as the size of the stomach diminishes, to say nothing of the condition of the suture lines. If the age of the patient, duration or recurrences of symptoms of obstruction, and low gastric acidity lead to the belief that cicatricial tissue or neoplasm is the cause of obstruction, operation is performed within a few days or a week. Otherwise, medical management is continued two or three weeks before a decision as to the need for surgery is made. Ordinarily, if the patient has had only one episode of obstruction due to duodenal ulcer and responds quickly to medical management, this form of therapy is continued.

The complications of duodenal ulcer have been mentioned. There remains a fourth group in which surgical procedures should have consideration. Reference is made to patients whose intractable symptoms due to duodenal ulcer fail to respond to adequate medical management, or persons who have considerable difficulty in following any type of medical regimen.

In the absence of pyloric obstruction due to cicatricial stenosis, and particularly if repeated hemorrhages have been present, many gastro-intestinal surgeons now favor partial gastrectomy and partial duodenectomy followed by reestablishment of gastro-intestinal continuity by the Billroth I or II method. This type of operation has proved satisfactory in our hands when it can be done with safety to the patient.

When the indications for surgery have been excluded, we believe prolonged medical management is in order. This applies to most of the patients with duodenal ulcer. We believe the *type* of medical treatment used is not as important as its *duration* and the *consideration of the health of the patient as a whole*. The same thorough supervised treatment that is given to the patient with diabetes, tuberculosis, or nephritis should be given to the patient with duodenal ulcer, even though symptoms are quickly relieved and the prognosis is far better. Because of the quick relief of symptoms, the problem is to secure the cooperation of the patient over a sufficient period of time, meaning several years, even though on a management formerly considered inadequate by authorities in this field.

Physicians who have duodenal ulcers do not, as a rule, cooperate as well as laymen *over a sufficient period of time*. Since the incidence of symptoms due to duodenal ulcer commonly is greater during the spring and autumn months, physicians often start taking frequent feedings and alkalis several weeks before the expected onset of symptoms. As a matter of fact, in most of the cases of uncomplicated duodenal ulcer we encounter, the end-result indicates that ambulatory methods of treatment are as effective as hospital management, provided we obtain over a long period of time the same cooperation that we are most likely to obtain in patients having preliminary hospitalization. When possible, the latter procedure is ideal, for it makes possible daily examinations of the stools for occult blood, gastric aspiration relative to neutralization of gastric acidity, as well as determination of the response of the individual to management and teaching the patient how to take care of himself. Accurate information relative to food and vitamin intake is also available. Either a ten-day period of management by the continuous aluminum hydroxide drip method^{8, 9} or the strict Sippy method, as modified by Brown,¹⁰

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CARCINOMA OF THE STOMACH

Any adult person who has had chronic dyspepsia for one month or longer should have at least one reliable roentgen examination. In our experience, the roentgen examination has been the most important single diagnostic procedure and in patients who have had exploration, the roentgen diagnosis has been confirmed in 95 per cent of the cases. Therefore, we believe the chief means of advancement in the cure of this disease is to make the roentgen examination a routine procedure in the cases mentioned. Earlier diagnoses must be made. Regardless of the details of the symptoms, a patient who is in the carcinoma age group and who has gastric symptoms should be considered as having carcinoma until proved otherwise. Eighty per cent of our patients were in the fourth to sixth decade inclusive, but a feature which should be emphasized is the fact that approximately 10 per cent were below the age of forty years. Gastric syphilis may need to be considered in the differential diagnosis although this lesion is exceedingly rare in our experience.

Carcinoma of the stomach is not a hopeless condition if detected early and if situated in the pyloric area. The size of the growth does not necessarily determine the extent of metastasis or operability. Small lesions may metastasize early while large lesions may metastasize late. If palpation does not reveal evidence of fixation, if rectal examination does not reveal evidence of a Blumer's shelf, and if there is no so-called "Virchow's gland" in the neck or other demonstrable metastases, we believe that the patient should have an exploratory operation, regardless of the size of the lesion. Although evidence of metastases or an unresectable lesion may be found at operation, gastro-enterostomy can usually be done, and the resulting comfort to the patient well justifies the procedure.

When carcinoma of the stomach involves the pars media or cardiac end of the stomach, the situation of the lesion usually means an unresectable lesion. When the lesion involves chiefly the pars media, it is usually an extensive lesion by the time the patient seeks medical attention, because of the lack of symptoms other than weakness, pallor, and loss of weight, which are late symptoms in carcinoma of the stomach. Roentgen therapy has not been a curative procedure in our hands.

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Total gastric resection has been done in a few instances, with encouraging results. The use of roentgen therapy may be considered in the hope that the lesion is a lymphosarcoma. Roentgen therapy has been curative in proved cases (biopsy) of localized lymphosarcoma.¹²

REFLEX CAUSES OF CHRONIC DYSPEPSIA

In our experience, *biliary disease* is not only the most common organic cause of gastric symptoms, but is the most common *organic* cause of pain in the abdomen in the adult. The presence or absence of one or more attacks of definite biliary colic, particularly if accompanied by jaundice, and the roentgen findings, have been the chief criteria on which we base the indication for surgical procedures.

Nonvisualization of the gallbladder by cholecystogram does not necessarily mean that the gallbladder is pathologic, even though the patient is fair, fat, aged forty, has had pregnancies, and has a gaseous dyspepsia, or even pain in the right upper quadrant of the abdomen. Functional disturbances in the colon have been a frequent cause of the symptoms mentioned and recheck cholecystography after the patient has been on bowel management have resulted in normal findings in many of these instances. This experience coincides with that of Lahey and Jordan.¹³ However, if the double-dose method of cholecystography¹ is used, nonvisualization of the gallbladder by cholecystogram, in our experience, usually indicates a non-functioning gallbladder containing calculi of the cholesterol type (70 per cent of patients undergoing operative procedures), often blocking the cystic duct. Consideration must, of course, be given to other causes of nonvisualization, such as diseases in the liver or in adjacent organs which may cause reflex disturbances in the dye-concentrating ability of the gallbladder or dysfunction in the sphincter of Oddi. Included in this group are active duodenal ulcer, functional disturbances in the colon, pancreatic disease, abnormality in the right kidney, or even simple achlorhydria.

When the patient gives a history of unquestioned *biliary colic* and the roentgen examination shows the presence of gallstones, the need for surgery is obvious. However, the incidental finding of gallstones in a patient who has had no

symptoms of biliary disease often seems to be a detriment to the patient, from the standpoint of apprehension in a neurotic individual if the gallbladder is not removed, and the fact that cholecystectomy in these instances may result in no benefit to the patient. The question of so-called "silent gallstones" is controversial. The indication for their removal will, of course, depend on many features. At least in elderly patients, their removal is usually not indicated.

A normally functioning gallbladder without evidence of stones, as revealed by cholecystography, does not mean that the biliary tract has been excluded as a cause of symptoms, but we do believe that convincing clinical evidence must be present in order to justify *immediate* surgery for biliary disease. The response to medical management is often gratifying in these instances as well as as in other instances where immediate surgical procedures are not used. Operation may be done at a later time if the response to treatment is not satisfactory. Use is made of the Twiss and Greene¹⁴ diets, but emphasis is placed on a reducing regimen for the overweight and a high calorie diet for the underweight. The intermittent use of antispasmodics and mild sedatives, as well as alkalis or hydrochloric acid and bile salt and acid preparations (containing no laxative) may be indicated. The most frequent indication in these instances is bowel management, the discontinuance of excessive saline laxatives, and the restoration of normal bowel function.

Reflex dyspepsia due to pathologic changes in the *appendix* may be encountered, particularly in younger individuals with an "ulcer-simulating" type of distress. If a detailed history does not furnish evidence of clear-cut, acute attacks of appendicitis, a complete roentgen examination of the gastro-intestinal tract as well as the use of other laboratory procedures are indicated before resorting to surgery.

Reflex dyspepsia due to primary disease in the *urinary tract* needs emphasis. Engel¹⁵ has mentioned that 30 per cent of our patients with lesions of the kidneys and ureters have gastro-intestinal symptoms and that 34 per cent of our patients with hydronephrosis have had previous abdominal operations without relief of symptoms. In 52 cases of hydronephrosis associated with aberrant artery, 26 per cent of the patients had been

treated for gastro-intestinal disease and 17 per cent had had previous abdominal operations without relief of their symptoms. Urinalyses in these instances may present normal findings. Another fact which must be kept in mind is that chronic diffuse nephritis with or without uremia may give rise to marked anemia, anorexia, nausea, vomiting, and loss of weight. Determinations of the blood urea and creatinine as well as tests of urea clearance and urine concentration (Mosenthal) may be significant. However, calculous disease is the most common abnormality in the urinary tract causing gastro-intestinal symptoms and this is the reason for our routinely making a film of the urinary tract before starting the gastro-intestinal series' roentgen examination. The film also serves as a "scout film" of the entire abdomen.

SYSTEMIC CAUSES OF CHRONIC DYSPEPSIA

The systemic causes of chronic dyspepsia are legion. The gastric symptoms which are associated with the many acute infectious fevers are well recognized, but chronic disease in the lungs, pleura, and cardiovascular system, as a cause of chronic dyspepsia, is sometimes forgotten. Although the patient with *congestive failure* may have discomfort or pain in the epigastrium and even visible jaundice, as well as anorexia, nausea, vomiting, and marked flatulence, emphasis should be placed on the fact that he also has dyspnea and cough. Ernstone¹⁶ has pointed out that although angina pectoris usually causes retrosternal pain which comes on after exertion or after a large meal, it may give rise to marked epigastric pain, and coronary thrombosis may simulate an abdominal emergency. He has mentioned many other causes of pain in the abdomen due to cardiovascular disease.

Allergy as a factor in gastro-intestinal disturbances is considered elsewhere in this clinic. Other systemic causes for chronic dyspepsia which must be enumerated in this discussion are diseases of the nervous system and diseases of the endocrine glands, such as exophthalmic or toxic adenomatous goiter and Addison's disease, as well as deficiency diseases, such as pernicious anemia, pellagra, and sprue. Patients with pernicious anemia or Addison's disease may present symptoms and clinical findings highly suggestive of carcinoma of the stomach.

The inhalation of noxious gases is becoming a common cause of dyspepsia.

FUNCTIONAL CAUSES OF CHRONIC DYSPEPSIA

When organic, reflex, and systemic causes of chronic dyspepsia have been excluded, there remains the large group of functional causes. Although organic causes are of most serious import, the functional causes are by far the most common causes of chronic dyspepsia and the accompanying disability may be greater than is the case with some of the organic diseases. The increased nervous tension and irregular habits incident to present-day civilization are, of course, prime factors.

Smith¹⁷ has shown that epigastric distress may be due to an irritable colon (unstable colon, mucous colitis) and this coincides with our experience. Irritable colon has been the most frequent cause of alleged "stomach trouble." The symptoms may be referred to any part of the abdomen, or they may shift from one part of the abdomen to another, and secondary gastric symptoms are often present. Although constitutional and neurogenic factors are common causes of this disorder, due regard should be given to the indiscriminate use of coarse diets (including bran) and long-continued use of irritating cathartics, enemas, or colonic irrigations. Constipation or diarrhea may or may not be present. Examination of the stool may reveal the presence of parasitic disease. Evidence of hypermotility of the gastro-intestinal tract is often obtained from the history because close questioning will reveal that the patient has liquid stools and the barium meal roentgen examination will show marked hypermotility; in fact the meal may have reached the left colon four hours after ingestion rather than requiring the normally much greater period of time. Helpful objective evidence is also obtained when the sigmoidoscopic or the barium enema roentgen examination or both reproduce the patient's abdominal distress. Not only does chronic irritation in the colon over a long period of time finally result in chronic dyspepsia, but the long-continued overemptying of the colon may also produce evidence of deficiency disease, due to lack of absorption of fluid and minerals, particularly calcium and vitamins.

The principles of treatment include discontinuance of

cathartics and large enemas, the use of a low residue diet at first to allow rest to the colon and relief of symptoms, and subsequent gradual addition of residue until the patient is on a well-balanced diet; more rest, regular hours and habits, including reestablishment of normal bowel habits. The use of a small plain water enema (not to exceed 1 pint), a glycerin or a soap suppository may need to be used each morning for the first week or two, or until the normal rectal reflex is regained. Although antispasmodics and mild sedatives may need to be used temporarily or intermittently, the avoidance of undue chemical and mechanical irritation and the reestablishment of common-sense habits of living are the chief features of treatment.

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ROENTGEN EXAMINATION OF THE COLON

JOSEPH C. ROOT

THE roentgen examination of the colon is of value, not only in the diagnosis of functional and organic lesions of the bowel, but it may also be of assistance in determining the outline of abdominal masses which lack sufficient density to be observed roentgenographically. Malignant neoplasms by this means alone may be found sufficiently early in their growth that surgical intervention may offer a cure to the patient. Hence, the study must be thorough and should include both fluoroscopic examination and radiography. If an early diagnosis is to be achieved, no aid can be overlooked. Especially valuable is the use of the double contrast method of examination by which air is injected after the usual barium enema is expelled.

The conditions in the colon which may be visualized by means of the roentgen ray and the opaque enema may be classified generally under three main headings: anomalies, functional disorders, and organic lesions.

ANOMALIES

While anomalies are of some interest they generally are of little or no clinical significance. In this group, variations in the length of the colon are probably the most common. In some individuals the colon may be quite short, while in others it may be so long and redundant that it may be very difficult to visualize all portions of it. There may also be considerable variation in position, either of the entire bowel or of some portion of it.

The cecum frequently is seen in an unusual position and this may have clinical significance because of the close approximation of the appendix. Due to three variations in development the cecum may be found in almost any location in the abdomen except the left upper quadrant. The first of these

variations is failure of the cecum to rotate. Depending upon the degree of rotation, the cecum may lie in any location on the right side from the liver to the right iliac fossa. The second variation is an unusually long mesocecum which allows the cecum a wide circle of mobility while the third is the rare anomaly of complete transposition of the viscera. In questionable cases of abdominal pain which may be due to an inflamed appendix in an unusual position, a barium enema may be of considerable aid in establishing the diagnosis. It is also very valuable for the surgeon to be cognizant of the anomalous location of any organ so that he may better plan his approach for its removal.

FUNCTIONAL

The term "functional" is used here in the usual sense, meaning a disorder in the function of the colon with no apparent organic lesion or change in structure. In this group, the atonic and spastic types of colon are of greatest importance. The atonic type fills slowly, the diameter of the lumen is increased, and poorly defined, rather shallow haustral markings are seen. Due to its atonicity, this type is apt to empty poorly and, as a rule, a good mucosal pattern is not seen in the film made after the enema is expelled.

The "spastic" or "irritable" colon occurs quite commonly and is of importance due to the many and varied clinical symptoms which it may produce. The symptoms in this condition may vary from mild cramps, generally shifting in location, to a pain which may simulate peptic ulcer or even gall-bladder disease. The patient with a spastic bowel is apt to have considerable distress during the administration of the enema and it should always be determined whether that distress is similar to the usual complaint. If it is, this fact should be noted in the report of the examination, since it will be of value to the clinician in instituting the proper treatment. From a roentgen viewpoint this type of bowel generally shows a lumen somewhat smaller than normal and the haustral markings are prominent. In those cases in which the condition has persisted over a long period of time, a somewhat characteristic feature will be seen. This appears as a contracted left colon and a dilated right colon and is due to an intermittent, partial obstruction.

Areas of spastic contraction are commonly seen and may be suggestive of a neoplasm. If these suggestive findings are persistent, it is well to repeat the examination after the administration of antispasmodics. The spastic colon should not be considered as a clinical entity until all possible etiologic factors have been excluded, since it may be secondary to kidney stones, gallbladder disease, pathologic appendix, etc.

ORGANIC LESIONS

DIVERTICULOSIS

Diverticulosis is perhaps the most common of the organic lesions noted during the roentgen examination of the colon. It has been present in approximately 7 per cent of all the colons we have examined, including patients of all ages and both sexes. This condition occurs much more frequently, of course, in individuals past middle life and is found most often during the fourth and fifth decades. The reason for this age grouping is apparent if the probable etiology and structure of the sacs are considered. The pouches usually consist of only the mucosal and serosal coats of the bowel, and they appear as herniations through the muscular coat, being more prone to occur where the vessels pierce the wall. Whether diverticula are congenital or acquired is a moot question but the preponderance of evidence tends to indicate that they probably are the result of the average wear and tear on the bowel with added age. In spite of their very thin walls, rupture is rather uncommon.

Diverticula of the colon usually are located in the sigmoid and descending colon although they may be seen throughout the entire contour. While they may appear as single lesions, they are generally multiple and will be found in groups in one or more locations. During the examination they are seen as small sacs protruding from the wall of the bowel. Frequently barium will be seen in the haustra and the appearance of this condition should not be confused with that of true diverticula. The film made after the opaque solution is expelled is the most helpful, as here can be seen the diverticula which are on the anterior and posterior walls as well as those which are on either side. A typical example of diverticulosis is shown in Fig. 51. The sacs are confined to the sigmoid and it will be noted also that in this region the intervening bowel appears to be ser-

rated which is frequently found with diverticula and is due to secondary spastic change produced by some irritation or inflammation in the sacs. Diverticula without inflammation probably produce no symptoms but must be considered as a potential source of infection or irritation from certain types of food or ingested particles of food such as small fruit seeds. The presence of diverticula should always be noted on the report so that the clinician may prescribe a suitable diet and be



Fig. 51.



Fig. 52.

Fig. 51.—Early diverticulosis of the colon. Characteristic pouches are seen in the sigmoid with spasm of the intervening bowel.

Fig. 52.—Obstructing diverticulitis. Apparent filling defect is seen in the sigmoid. Distal to this area, small diverticula are seen. Film made in sigmoid position.

aware of the condition should symptoms of irritation of the bowel arise.

When there is inflammation within the sacs, diverticulitis will produce definite clinical symptoms ranging from mild spasm and cramplike pains to complete obstruction of the bowel at the site of the inflammation. An obstructing diverticulitis is seen in Fig. 52, the lesion being located in the sigmoid which is the usual site for this complication. It will be noted in this illustration that the appearance is suggestive of

carcinoma and it is from this lesion that the main differentiation must be made. As a rule, obstructing diverticulitis involves a fairly long segment of bowel, whereas a carcinoma in this region is apt to be rather short in length, with better defined and more prominent borders. The fluoroscopic examination is important in making a differentiation as one can palpate the lesion and determine whether it is fixed or movable, and whether pain is elicited on pressure over the area. The lesion of diverticulitis is tender and is generally fixed due to the inflammatory changes around the bowel. Carcinoma, on the other hand, is not usually tender and, in the early lesion without extension to adjacent tissues, is freely movable. Visualization of even a single diverticulum in this vicinity is of great aid in establishing the diagnosis, and care should be exercised to make a careful search for this condition. The absence of diverticula does not, however, exclude the diagnosis of obstructing diverticulitis, as the diverticula may not always fill with the opaque solution due to inflammatory changes or because they may contain fecal material and hence will not admit the barium. In questionable cases there should be no hesitation in rechecking the colon by means of another barium enema as the sacs may be visualized at a subsequent examination even though they did not fill during the original examination. At times the diagnosis of obstructing diverticulitis may present a difficult diagnostic problem but it is a most important one because the prognosis and treatment in comparison with that for carcinoma are much different.

Benign stricture of the intestine, such as may occur following radiation of a carcinoma of the uterine cervix, should also be considered in the differential diagnosis since the appearance of the two lesions may be similar. In this condition, however, the history will indicate the correct diagnosis.

CANCER

In this discussion of cancer, both carcinoma and sarcoma of the bowel will be considered. This term is used in preference to malignant disease because cancer refers to a malignant neoplasm. Malignant disease, on the other hand, is a misnomer since it may include any disease or lesion which is capable of rendering harm to the patient or producing injurious

effects. We are, of course, most interested in carcinoma since it is the most common type of neoplastic disease found in the colon.

Roentgenographically, carcinoma is characterized primarily by definite and permanent filling defects in the lumen of the bowel with marked destruction and alteration in the mucosal pattern. While variations in size and contour may be produced, the growth will always be found to be adenocarcinoma, even though in some sites it appears to be quite smooth and resembles a scirrhus lesion. The answer to this will be found in the size of the lumen of the bowel and in the nature of the contents of the bowel at the location of the lesion. In the cecum, for example, the growth may be quite extensive and may involve the entire caput at the time of the examination because a comparatively long period has elapsed between the inception and the time when symptoms or signs are sufficiently severe to call attention to the possible presence of a neoplasm. Obstruction in the right side of the colon, because of the large lumen and liquid contents, is not produced until late in the course of the disease unless the ileocecal valve is involved. As a result, the patient or the physician may not become aware of the lesion until it is far advanced, since the onset is insidious and early signs may be only a slight loss in strength with an anemia which might easily be ascribed to some other cause. In Fig. 53 is shown an advanced carcinoma of the cecum with a marked and definite filling defect. It is interesting that, even though this patient was a physician, the onset was so gradual and insidious that he was not aware of the true nature of his condition, the colon examination having been carried out as a part of the routine examination. With such an extensive lesion a mass is present of course, although it may not always be palpable due to the size of the patient, the condition of the abdominal wall, etc.

As the size of the lumen of the bowel decreases toward the terminal end and as the contents become more solid, the growth produces an obstructing lesion proportionately earlier in the course of the disease. Here, too, the lesion will be smaller and in the typical cases the filling defect has a characteristic "napkin-ring" appearance as shown in Fig. 54. It should be noted here that the ends of the lesion are well defined and it

is not difficult to determine the type of pathology that is present. Particular attention is directed toward the appearance of the mucosal pattern. In this film it is readily seen that the mucosal pattern is entirely obliterated and no markings are present, this being due, of course, to the fact that carcinoma is principally a lesion of the mucosa. A very early carcinoma in the region of the splenic flexure, which has not progressed to involve the entire lumen is demonstrated in Fig. 55. This film was made after the injection of air following expelling of the enema and



Fig. 53.



Fig. 54.

Fig. 53.—Adenocarcinoma of cecum. There is a marked filling defect in this advanced lesion, chiefly in the region distal to the cecal valve.

Fig. 54.—Adenocarcinoma of transverse colon. A characteristic "napkin ring" filling defect is shown. The features in this lesion are the complete absence of mucosal markings and well defined ends.

it shows the tumor projecting into the lumen of the bowel. This type of double contrast examination is a very valuable procedure, as shown in this case, and will be described in detail later in the text.

Sarcoma of the colon, while relatively uncommon, does occur with sufficient frequency to constitute a diagnostic problem. Figure 56 shows the changes which should make one suspicious that sarcoma rather than a carcinoma is present. In this film is seen a filling defect which at first impression

suggests a malignant neoplasm. The sarcoma, however, originates in the submucosa of the bowel while the carcinoma starts in the mucosa. Hence, it would be expected that the mucosal pattern would be altered to a lesser extent, if at all. In this film the mucosal pattern, which has not been invaded, serves as a valuable diagnostic guide. The sarcoma, as a rule, responds



Fig. 55.



Fig. 56.

Fig. 55.—Early adenocarcinoma at splenic flexure. Film made after air injection. The barium-coated lesion can be seen projecting into the lumen of the bowel.

Fig. 56.—Sarcoma of colon. Marked filling defect, yet the mucosal markings show little deviation from normal. This lesion is in contrast to that shown in Fig. 54.

to roentgen therapy, a point that will assist in the diagnosis if operation is not feasible.

TUBERCULOSIS

Tuberculosis of the gastro-intestinal tract is a common complication in open advanced pulmonary tuberculosis. From autopsy findings it has been estimated that the incidence may run as high as from 50 to 80 per cent and the usual site of involvement is the ileocecal region. Primary tuberculosis of the intestinal tract may occur but it does so with relative in-

frequency and is usually the hyperplastic type. In the colon, tuberculosis usually appears as an ulcerative or hyperplastic lesion, but it may be evident as an infiltrating process of the wall, although this type is uncommon.

The ulcerating type of tuberculosis manifests itself during the roentgen examination as a spastic filling defect due to the extreme irritability of the part of the bowel involved. During the fluoroscopic examination, the part may be observed to fill but immediately to empty again due to the spastic contraction.



Fig. 57.



Fig. 58.

Fig. 57.—Tuberculosis, ulcerating type. A typical spastic filling defect is seen in the cecum. Terminal ileum also involved and shows a marked narrowing.

Fig. 58.—Tuberculosis, hyperplastic type. Filling defect seen in cecum which must be differentiated from carcinoma.

In the films, the part will always be empty of barium although the solution may be present on either side. A spastic filling defect in the cecum, caused by an ulcerating tuberculous lesion, is demonstrated in Fig. 57. This area was void of the opaque solution in all the films made during the examination. In addition to the spastic filling defect in the cecum, there will be noted a distinct narrowing of the terminal portion of the ileum which also was involved in the process.

The hyperplastic type of tuberculosis is characterized, from the roentgen viewpoint by a definite and permanent fill-

ing defect in the portion of the bowel involved. This may resemble the filling defect produced by a neoplasm and, from the roentgen evidence alone, it is extremely difficult, if not impossible, to differentiate the two lesions. It has been stated by some observers, however, that there is something in the nature of a physiological sphincter near the ileocecal valve and that it is at this point that carcinoma develops, whereas tuberculosis tends to develop at the lower pole. Hence, in carcinoma there is apt to be a division of the cecum by the ingrowing mass, whereas in tuberculosis the lower pole becomes more or less obliterated by the growth of the hyperplastic tubercle. While the region of the ileocecal valve may show a great number of carcinomas, this theory cannot be accepted as a definite differentiating point in the diagnosis since we have frequently seen early hyperplastic tuberculous lesions which have developed at the same point. In Fig. 58 is shown a hyperplastic lesion of tuberculosis involving the cecum. The filling defects noted in this case were quite prominent and might well have been interpreted as due to a carcinoma. Subsequent examination eight months after the original examination showed almost complete obliteration of the cecum with a partial obstruction developing at the ileocecal valve.

In general, the diagnosis of hyperplastic tuberculosis of the colon should not be made from the signs noted during the roentgen examination of the colon alone. The physical condition of the patient should be taken into consideration as well as the degree of anemia which is present. The patient with a hyperplastic tuberculous lesion may appear to be in quite good health as contrasted to the size of the lesion and the advanced stage of the disease, whereas the patient with carcinoma will show general debilitation and generally a marked anemia. A film showing pulmonary tuberculosis is, of course, a great aid in the diagnosis since, as has been pointed out, primary tuberculosis of the gastro-intestinal tract is uncommon in the absence of a pulmonary focus. A knowledge of the age of the patient is of value, as tuberculosis is usually found in young individuals as contrasted with carcinoma which is more common in patients past middle life.

ULCERATIVE COLITIS

In the early stage of chronic nonspecific ulcerative colitis, the colon may show nothing more than an increased spasticity and perhaps a little irregularity of contour along the walls. In the more advanced phase, there will be seen the characteristic finding of the straight rigid walls due to infiltrating changes. The haustral markings are absent in the filled colon and, in the films made after expelling the enema, the rigid character of the walls is marked, together with a lack of normal mucosal markings. The infiltration of the walls not only



Fig. 59.—Ulcerative colitis. To be noted here is the smooth, nonhaustrated appearance of the sigmoid and the contracted rectum. This is an early lesion and the remainder of the colon appears to be normal.

decreases the lumen of the bowel, but some degree of shortening over that considered as normal will be apparent. The colon seen in Fig. 59 demonstrates these features in an early lesion involving the sigmoid and rectum, with normal contour in the right half. During the fluoroscopic examination in such cases, it will be noted that the involved parts fill rapidly, the barium solution literally shooting through the rigid walls with no haustra to impede its progress. Contrary to what might be expected, however, no hypermotility in the colon is shown in the progress films made when the barium meal is admin-

istered orally; rather, there will be a slowing in the passage of the barium through the affected areas.

Ulcerative colitis may occur in patients in any age group, but it is found more commonly perhaps during early and middle adult life. In 95 per cent of the cases the rectum is involved first with spread by continuity toward the proximal end of the colon. The diagnosis may thus be made in this group of cases by the typical changes found in the mucous membrane by means of a proctoscopic examination and determination of the extent of the lesion by means of the roentgen examination. In the remaining 5 per cent of the cases, the rectum is not involved and the disease may originate in any part of the colon and be limited to a single area, or there may be multiple areas with normal colon intervening. In this group, the diagnosis cannot be made by proctoscopic examination, but the presence of blood and mucus in the stool will be an aid in establishing the final clinical diagnosis of chronic ulcerative colitis.

In the far-advanced stages of the disease there may be formation of polyps either singly or a generalized polyposis of the entire involved area may develop. These in turn may show malignant degeneration and a typical carcinomatous progression.

Amebiasis has been reported to produce characteristic roentgen findings, such as shortening of the right colon together with infiltration of the wall and a decrease in the diameter of the lumen. These signs may be present in some cases but we have not been able to demonstrate them consistently enough that they may be considered a diagnostic criterion. In many of our cases of proved amebiasis, no abnormal changes in the colon have been seen by means of the roentgen examination. On the other hand, amebiasis must always be considered when signs of right side ulcerative colitis are present.

POLYFOID LESIONS

Under this classification is included any organic lesion of the colon which projects into the lumen; hence, it may include both the benign and early malignant lesions which show this characteristic. For the roentgen diagnosis of these conditions, it is essential to employ the double contrast method of in-

jecting air into the colon after the opaque solution has been expelled. If this technic is not employed, lesions may be entirely missed by the ordinary method of examination due to the possible small size of the pedicle at the mucosal junction. An example of this is shown in Figs. 60 and 61. This patient was found by physical examination to have a carcinoma of the rectum and the examination of the colon was ordered to determine whether there might be any lesion proximal to



Fig. 60.



Fig. 61.

Fig. 60.—Carcinoma of rectum. A characteristic filling defect with no evidence of polyp formation.

Fig. 61.—Preceding case after evacuation of opaque solution and injection of air. A barium-coated polyp is clearly demonstrated by means of the double contrast technic.

that found in the rectum. In the first film (Fig. 60) may be seen the filling defect produced by the carcinoma but there is no evidence of any polyp. The second film, made after the injection of air shows very clearly a single polyp to which the barium has adhered and which is made more prominent by the contrast of the air media.

Polyposis of the colon, in which there are multiple small polyps, is an infrequently encountered condition and one which may involve the entire colon or a portion of it. The

appearance is marked by the many small, globular, grapelike projections extending into the lumen. The normal mucosal markings are completely obliterated, showing instead irregular markings produced by the collection and retention of the opaque solution in the depressions between the polypi. In the filled colon, there may be multiple small filling defects, and these are more pronounced if the lesions are discrete. The incidence of malignancy in polypoid lesions will roughly be in a direct ratio with the number of polyps present. The single polyp will probably be benign, whereas in a generalized polyposis a high incidence of neoplastic degeneration may be expected.

TECHNIC

For a proper examination of the colon by means of the roentgen ray and an opaque solution, we believe that the preparation of the patient is of paramount importance. When the patient is properly prepared no confusing shadows will be formed by fecal material within the bowel. In a clean bowel, one may immediately proceed with an air injection if there is any indication for it but this examination is of no value whatever if inspissated fecal material be present. Our routine method of preparation is to administer an average dose of 1½ ounces of castor oil the day preceding the examination. This is followed, where possible, by a cleansing enema administered early on the morning of the examination. If contraindications to the use of the oil be present, cleansing enemas are given until the return is clear. It will be found, if the preparation is thorough, that not only will confusing shadows be absent, but that during the fluoroscopic examination the colon may be more easily manipulated and with more satisfactory visualization of the flexures.

In our routine examinations, we employ a solution of barium and water to which is added acacia solution and a sufficient tannic acid powder to make a 1 per cent concentration. This has proved very satisfactory in our hands and shows good mucosal patterns on the film made after expelling the enema. Special preparations of colloidal thorium dioxide are available and have been advocated as of particular value in showing the mucosa, but we have had little experience with them. The barium solution should be well mixed and warmed

to body temperature. The rate of flow should be a moderate one, stopping momentarily if the patient experiences discomfort. The tubing from the can should contain a valve, allowing the solution to flow in one direction only, thereby avoiding contamination of the solution remaining within the container.

The solution should be administered under fluoroscopic control, so that the colon may be properly filled and small

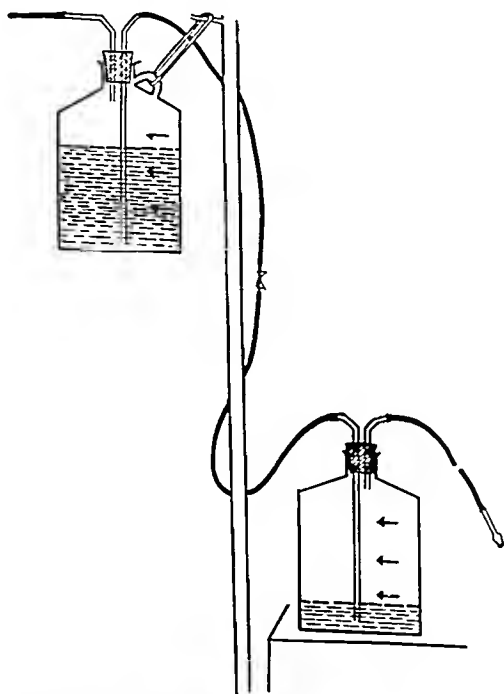


Fig. 62.—Diagrammatic drawing of air injecting apparatus. Water syphoned into lower container from the upper, forces air into the bowel at a steady, constant pressure.

lesions noted before they are completely obscured. The patient should be rotated on either side as indicated, as it is only by this method that the entire colon and especially the sigmoid region may be visualized. The use of a bulbar rectal tip is useful in this connection as the possibility of the tip coming out of the rectum is lessened. Palpation is a necessary procedure, not only to determine areas of tenderness but to straighten out the flexures in order that they be visualized

completely. It is our routine practice to make one film with the colon filled and one film after the solution has been expelled. If it is suspected that the disease is in the sigmoid, only a small amount of the barium solution is used, and special films are made before the area is obscured. These are made by placing the patient on the back with the left side on the table and the right side elevated so that an angle of forty-five degrees is formed. The film made after expelling the enema is very important as it is here that the mucosal pattern is shown, making possible the diagnosis of early lesions.

When an air injection is to be made, the patient is examined under the fluoroscope to determine whether sufficient barium has been expelled, as it is desirable that only as much barium remains as will be needed to coat the interior of the bowel. The air is injected by means of the apparatus shown in Fig. 62. This consists of two, 1-gallon glass jugs with tubing as shown in the diagram. The sides are marked in quarters so that, as the water flows from the upper to the lower container, the approximate amount of air injected may be determined quickly. The injection of the air is likewise made under fluoroscopic control, allowing to flow in only a sufficient quantity to completely fill the colon. After the colon is satisfactorily filled with air, an additional film is made to show the distended bowel by the double contrast thus obtained. A practical point to be considered is that this film should be made with less density than the usual colon film.

SUMMARY

Typical lesions of the colon have been considered and illustrated in the hope that early diagnoses may be made in the presence of these conditions.

A routine method of examination has been suggested with emphasis upon the proper preparation of the patient which is of paramount importance.

The double contrast technic should be used when indicated, particularly for diagnosis of the polypoid lesions. A simple, efficient means of injecting air into the colon has been demonstrated which provides a constant flow of air, the quantity of which can be measured.

RECENT CHEMOTHERAPEUTIC ADVANCES IN THE TREATMENT OF INFECTIONS OF THE URINARY TRACT

C. C. HIGGINS AND F. C. SCHLUMBERGER

THE relative success of combating infectious diseases with chemotherapeutically active substances seems to depend to a large extent upon the structure of the pathogenic organism. The spirochete, which belongs to the bacteria group, and those organisms which belong to the protozoa group represent highly differentiated species. The higher the development of a pathogenic organism, the more vulnerable it is to the action of chemotherapeutic substances.

As yet we have no chemotherapeutic substance which is active in the virus diseases and, until recently, we had no specific substance with which to combat bacterial infections due to cocci and bacilli. These two types of infective organisms occupy the lowest level in the classification of microorganisms. Up to the present time, the search for a bactericidal substance has yielded only a group of highly efficient disinfectants but not a single substance which can be used for the destruction of organisms actually invading the body.

As early as 1917 it became known that the hydrogen ion concentration of the urine affected the growth of bacteria. This resulted in the administration of acidifying agents to reduce the pH of the urine to a point where it was most bacteriostatic. In 1931 the ketogenic diet was introduced. Its use produced a highly acid urine and also a substance which was definitely bacteriostatic. This led to investigations which revealed that beta-oxybutyric acid was the effective agent. Oral administration of the substance, however, proved it to be unsatisfactory since it is completely oxidized before it is excreted by the kidneys. This induced Rosenheim¹ to search for a substance which would combine bacteriostatic properties

and yet be unaltered by metabolic processes. Continued investigation led to the use of mandelic acid which had been shown by Shotten² in 1883 to be eliminated in a completely unaltered state in the urine of dogs. This chemotherapeutic agent has proved to be of great value in the management of urinary infections.

More recently, considerable research which has been done largely in Germany, showed that the azo compounds possessed a relatively effective action on bacteria in vitro. Domagk³ observed a certain activity on the part of azo compounds containing sulfonamide in the streptococcal sepsis of mice. This was the important starting point for the development of a new chemotherapeutic agent which was to become highly effective in the bacterial group. Para-amino-benzene-sulfonamide, more conveniently designated sulfanilamide, is the second addition to our chemotherapeutic armamentarium.

Mandelic acid is an aromatic hydroxy acid which is known chemically as hydroxyphenylacetic acid. Its therapeutic use in infections of the urinary tract followed the successful employment of the ketogenic diet in the treatment of similar infections. The ketogenic diet requires the most careful management if good results are to be obtained. Its administration often causes distressing general and gastro-intestinal symptoms while mandelic acid therapy obtains similar or perhaps better results and is, on the other hand, much less complicated from the administrative standpoint.

The results reported on the use of mandelic acid indicate that the drug has definite value and that it is superior to many other forms of medication for treatment of certain urinary infections. Recently, Carroll, Lewis and Kappel⁴ reported that normal urine was found in 49 of 50 cases of *Bacillus coli* infection following therapy with mandelic acid for two to twenty-four days. This therapy was combined with an acid-ash diet and the use of ammonium chloride to attain the proper urinary pH. In this series the urine of all but 9 patients was rendered sterile on culture. Less success was experienced with the *B. proteus* infections and the staphylococci group. Cook and Buchtel⁵ report sterilization of the urine in 80 per cent of the uncomplicated cases of bacillary infections of the urinary tract.

In our experience we have found mandelic acid very applicable in bacillary infections of the urinary tract, apparently being most effective against the colon bacillus. Less satisfactory results have been obtained when the staphylococcus and *Bacillus proteus* were present. Approximately 76 per cent of uncomplicated cases of colon bacillus infection of the urinary tract responded favorably to this form of therapy. The urine in these cases was rendered sterile within four to fourteen days, an average of approximately eight days being required. In 11 cases in which staphylococci were present in the urine, less promising results were obtained. In only three instances did the urine become sterile and the remainder of the patients experienced only symptomatic relief. In the patients with a proteus infection, the response was unsatisfactory as the elimination of this organism from the urinary tract is most difficult. This, of course, is due to the fact that the pH of the urine cannot be rendered sufficiently low and hence the bactericidal power of the therapeutic agent is diminished. This evidence has recently been substantiated by Helmholtz.⁶

In the successful cases we have had, symptomatic improvement usually occurred after mandelic acid had been administered for a few days, although a longer time was required to render the urine actually sterile. The most rapid improvement in the clinical condition of the patient was observed when a colon bacillus pyelitis or cystitis was present. In such instances, the toxic effects disappear rapidly and the frequency of micturition and dysuria becomes less, even though the urine may still be infected. The lessened irritability of the bladder may be taken as an indication of the progress of the treatment. A great many patients in whom it was necessary to use retention catheters, who had infected sinuses, pyelitis of pregnancy, or other urinary tract pathology were symptomatically relieved but were not made free from bacteria and pus. It must, of course, be realized that the pyuria is only a manifestation of the existing pathology. In order to procure urine sterile and free from pus, the cause must be removed. In this respect mandelic acid becomes a valuable preoperative therapeutic agent. When it has been used following transurethral resection, the response has been favorable but much more slow than in cases of pyelitis.

It may appear that this form of therapy is very simple, but this is not the case. Unless the patient follows instructions in every detail and is checked daily by his physician, disappointing results may be obtained. We have found the following routine to be most applicable in carrying out essential points in the administration of this therapy: (1) daily dosage of the drugs, (2) total fluid intake, and (3) the degree of urinary acidity. Numerous preparations are available, but we have found that 12 Gm. of mandelic acid, given in doses of 3 Gm. each four times daily, constitutes an adequate amount. One liter of water per day should be allowed. This must be properly rationed through the twenty-four-hour period in order to maintain as nearly constant as possible the urinary concentration of mandelic acid. The urine, by whatever means necessary, should be kept at or below a pH of 5. This is a prime requisite in order to obtain full therapeutic response. The patient should be cautioned against taking foods which might produce an alkaline urine. Ammonium chloride in enteric coated tablets has served well in maintaining the pH at the desired level. The ketogenic diet or acid-ash diet may also be employed for this purpose. For proper control, it is obviously necessary that a cell count of the urine and a determination of the pH should be done daily. The duration of the treatment should be from fourteen to sixteen days during which time satisfactory results should be obtained in the majority of cases. Our policy has been to use intermittent therapy in the treatment of resistant or complicated cases. It has been suggested that if the bacteria are not eliminated rapidly, they may in the course of time become more resistant to the therapeutic agent. Recurrent infections appear to respond favorably to intermittent, short courses of treatment and the patients experience much symptomatic relief.

The administration of the drug is sometimes accompanied by a few unpleasant symptoms. Gastro-intestinal upsets are perhaps most commonly experienced. Nausea was noted in about 8 per cent of our cases and on several occasions vomiting occurred. This can be controlled largely by administering the drug after meals and perhaps in some instances it may be necessary to begin with a smaller dose or give the drug less frequently. Some patients who were receiving an adequate

dosage experienced diarrhea, as many as 4 to 6 stools occurring each day. In such instances, the amount of medication taken each day must, of course, be reduced until it is better tolerated. Other general reactions were headaches and tinnitus, but these were less severe in character. Such reactions can be controlled, as a rule, without altering the regular routine. Skin reactions have rarely been experienced, but, when met with, usually necessitate discontinuance of medication. Evidence of renal irritation was encountered in a few cases. This was indicated by the presence of red blood cells in the urine and on one occasion hyaline casts were noted. Gross hematuria was observed in none of our patients. Renal irritation was only of a temporary nature as the findings disappeared quickly as soon as the drug was discontinued. A mild elevation of the blood urea was observed in about 50 per cent of the cases. In patients in whom there is renal insufficiency, the drug should not be administered. Whenever any of these reactions occur, continued treatment should proceed with extreme care.

More recently there have been striking reports of the beneficial results following the use of sulfanilamide (prontylin) in streptococcus infections in man. This substance was first introduced into the United States by Long and Bliss⁷ of Baltimore. Encouraging, also, are the results obtained with this drug in the treatment of erysipelas, peritonsillar abscess, meningococcus meningitis, and pneumococcal infections. This made it seem worthwhile to determine its possible efficacy as an antiseptic in the urinary tract. Prontosil was used extensively at first until it was found that para-amino-benzene-sulfonamide was excreted and was probably the active principal, since then prontylin (para-amino-benzene-sulfonamide) has been in more general use.

It should be realized that larger series of cases must be followed over longer periods of time before a complete evaluation of this new method of treatment can be made. We feel, however, that the urines of patients taking sulfanilamide develop definite bacteriostatic or possibly bactericidal power for the organisms commonly present in infections of the urinary tract.

Infections of the upper urinary tract and bladder responded

favorably to sulfanilamide in a large percentage of cases. Cultures of the urines in this group of patients showed the following organisms to be present: the gram-negative group of bacilli, staphylococci, mixed infections of colon bacilli and cocci, and the streptococcus. Oral administration of the drug was employed in all the cases with the exception of one. In this group of patients, a favorable response was obtained in from fourteen days to three weeks. The response was more prompt in the bacillary group than in the coccal group. One patient who had an infection of the upper urinary tract—the offending organism being a streptococcus—was unable to take the drug orally, so intramuscular injections of prontosil were given with a most favorable response. On two other occasions, the drug was not tolerated and only small doses were administered with occasional periods of rest. These types of infections occurred most frequently in patients in the older age group, and there was a wide variation in the toleration of the individual patient to the drug. We feel, therefore, that sulfanilamide should be used in infections of the upper urinary tract only after the infection has failed to respond to other urinary antiseptics, including mandelic acid and other methods of treatment. Favorable results have been reported by Kenny⁸ and his associates in the treatment of infections of the upper urinary tract during pregnancy. We have hesitated to use the drug for these patients since its toxicity, both on the patient and on the fetus, are not definitely established. In younger patients in whom the incidence of gonorrhea is higher, reactions did not occur as frequently as in the older patients. Usually 30 to 40 grains were given daily for a period of six to twelve days. During this period adequate bacteriostasis was produced and the urine was rendered sterile in many cases. Therapy was then continued, however, reducing the daily administration to 15 to 20 grains or in some cases the same amount was administered every other day to guard against recurrence of the infection. If the patient is extremely ill and unable to take the drug orally, it may be given as a 1 per cent solution in physiological saline, as a subcutaneous infusion the initial dose for adults being 300 to 400 cc. or 3 to 4 Gm. of sulfanilamide.

The administration of this drug is perhaps more simple

than that of mandelic acid since its effectiveness, as far as has been determined, is not dependent upon obtaining a satisfactory level of the pH of the urine. The patient may be allowed to continue on his regular diet and daily habits although bed rest in many cases is desirable. The fluid intake should be constant and not excessive as the drug is quickly eliminated through the urinary tract when large quantities of fluid are taken. If severe symptoms of toxemia develop, large amounts of water should be given, since the greatest portion of the drug is eliminated through the urinary tract. It has also been shown that saline cathartics should not be used during the administration of sulfanilamide, as sulfhemoglobinemia may result.

Infections of the lower urinary tract have responded to sulfanilamide even more strikingly than those of the upper urinary tract. Favorable responses have been obtained in the treatment of chronic prostatitis of the nongonorrheal type. In this respect, the drug (20 to 30 grains daily) has been used as a supplement to the usual routine we employ in treating nonspecific chronic prostatitis. Little attention has been given to the causative bacteria but we have noticed a much more rapid reduction in the number of pus cells in the prostatic secretion and the patients have enjoyed early symptomatic improvement.

In the treatment of acute and chronic gonorrhea, varied results have been obtained. One observation has been quite constant—in both the chronic and acute cases, the initial response of the patient is the keynote to the entire course of the disease. In our experience, if the patient responds promptly to adequate therapy, a rapid cure usually results; if, however, the initial response is delayed, the entire course will be considerably prolonged. Of 14 patients with chronic gonorrhea, which had been present from three weeks to four months, 9 were cured within from eleven to twenty-six days. Two of the 14 patients discontinued treatment and 3 had recurrence of the discharge when the drug was discontinued. These, however, responded promptly when treatment was resumed.

In 21 cases of acute gonorrhea, a quick response to sulfanilamide was noted in 9 instances; all urethral discharge

disappeared in five days, and smears were negative for gonococci. In 4 cases, there was prompt reduction in the amount of discharge but gonococci did not entirely disappear until the twelfth day of treatment. In the remaining cases, the discharge subsided slowly, and in several instances recurrence of the discharge was noted after the medication had been discontinued. In several cases in which there was no discharge, numerous gonococci were present in the shreds and urine sediments. In all cases prompt symptomatic relief was noted, burning and frequency subsided immediately, and in no instance was there progression of the infection or evidence of any epididymitis. Inasmuch as gonorrhea occurs most frequently in patients in the young age group, a larger dosage of the drug can be administered. We believe that 60 to 70 grains of sulfanilamide should be given the first three days and then a maintenance dosage of 30 to 40 grains daily. A number of patients received prontosil intramuscularly and prontylin orally but the response was no more striking than in those patients who received the drug orally. The patients were asked to observe the usual precautions and dietary measures employed in treating gonorrhea, and saline cathartics were eliminated. No local treatment was given until the organisms were definitely absent.

Reactions to the administration of this drug have been reported in several instances, chiefly sulfhemoglobinemia, agranulocytosis, hemolytic anemia, methemoglobinemia, and acidosis. The most severe reactions encountered in our series have been a marked cyanosis which was present in a few cases and acidosis which occurred in two cases.

Long and Bliss⁷ believe the cyanosis can be disregarded. Bicarbonate of soda has not been used routinely as advocated by Long and Bliss, but has been used successfully in combating acidosis in these cases, approximately 10 grains of bicarbonate of soda for each 10 grains of sulfanilamide being given. We have not seen any cases of hemolytic anemia or agranulocytosis which are the two complications most to be feared. Cutaneous eruptions have recently been reported by Goodman and Levy,⁹ and Bucy¹⁰ of Chicago has noted toxic optic neuritis. A feeling of lassitude and dizziness was not uncommon during the course of treatment. In several instances, nausea was experienced and on two occasions, vomiting was present.

Complete blood counts were checked every other day but there was no appreciable change in either the red or white blood cell count. A determination of the blood sulfanilamide is made daily and in severe infections the concentration is maintained between 10 and 12 mg. per 100 cc. This new therapeutic agent is said to be relatively nontoxic, but one must evaluate the reaction of the patient and accordingly regulate or completely discontinue the drug. Certainly, all patients should be under close observation during its administration.

CONCLUSIONS

1. We have added to our chemotherapeutic armamentarium two substances, strongly bactericidal (one possibly only bacteriostatic) to organisms usually found in infections of the urinary tract.

2. Both are easily administered but necessitate close observation and management of the patient in order to obtain proper results and to observe untoward reactions, the significance of which has not definitely been established.

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THE DIAGNOSIS AND TREATMENT OF PERIPHERAL VASCULAR DISEASE

JOHN TUCKER

THE peripheral blood vessels have two main functions—to carry an adequate supply of blood to and from the tissues and to assist in the regulation of body temperature. Under normal conditions, these physiologic processes go on without any conscious effort. The sympathetic nervous system and the circulating hormones of the blood regulate the degree of contraction or relaxation within the capillary bed and in this way control the minute volume of blood to any given area of the body. Disturbance in this automatic mechanism is most apt to occur in the extremities and especially in the legs. Several factors may act to localize the symptoms in the lower extremities: (1) the greater distance from the heart; (2) the effect of gravity on the venous return; and (3) the more exposed position of these structures. When the amount of blood flow per minute falls below a critical level, two chief discomforts are experienced—pain and coldness of the part. Very frequently the patient consults a specialist in shoe fitting who, in turn, convinces him that he has strain in his arches and that he will be relieved by orthopedic shoes and the use of some fine arch supports. Later, of course, the sufferer finally seeks the advice of a physician who can show that the trouble is due to circulatory inefficiency and not to mechanical strain. Fully three-fourths of our patients with peripheral vascular disease register for service in the Orthopedic Department when they first enter the Clinic.

Before the common peripheral vascular diseases are discussed in some detail, it is necessary to give a brief summary of the various physiologic and pathologic factors which cause this disease state. Three main factors are responsible for most

disturbances in the peripheral circulation: (1) excessive and prolonged vasospasm, (2) inflammation of the vessel walls, which often extends to include arteries, veins, and nerves, and finally (3) degenerative vascular changes due to the wear and tear of life. Broadly speaking, all the usual clinical conditions can be classified under these three headings. In the vasospastic group something has occurred to cause excessive tone of the sympathetic nerves. As will be shown later, a typical example of this is Raynaud's disease. In the second division, designated as inflammatory disturbances, we find thrombo-angiitis obliterans or Buerger's disease, and finally in the third or degenerative group are the various grades of arteriosclerotic changes in the extremities. The purpose of this paper is to simplify as far as possible the accepted ideas about several of these disease states, with particular reference to diagnosis and treatment.

In conditions of health, the tone of the peripheral blood vessels is not constant. It varies from moment to moment and is particularly influenced by the temperature of the external environment and the internal heat of the body. The state of the emotions as well as several miscellaneous factors such as the spastic effect of tobacco smoking, the reflex vasodilatation of the capillaries in the feet when an arm is put in warm water, and the temporary spasm or dilatation that results from a local injury to a leg or arm, the so-called "axon reflex" of Sir Thomas Lewis,¹ all modify the flow of blood in the peripheral vessels. While certain hormonal influences in the circulating blood may produce spasm or relaxation of the arterioles and capillaries, the major spastic effect occurs through the sympathetic nervous system. The postganglionic sympathetic fibers accompany the spinal nerves into the extremities and supply not only the blood vessels but also the sweat glands and the erectile muscles of the hairs of the body. For example, if the peripheral nerve to any part is severely damaged or cut, we observe not only anesthesia over the distribution of that nerve but also a distinct loss in vascular tone. This is due to the fact that the sympathetic fibers accompany the main nerve trunks to the feet and hands and are then distributed to the arterioles and capillaries.

In brief, the various agents that influence the tone of the

capillaries may be classified as either vasodilators or vasoconstrictors:

(A) Vasodilators:

1. Tissue metabolites formed during muscular work—carbon dioxide and increased hydrogen ion concentration.
2. Tissue extracts—histamine which produces capillary paralysis and increased permeability.
Choline which stimulates the vagus nerve, diminishes cardiac activity, and produces peripheral dilatation.
Adenylic acid which slows the heart and effects vasodilatation.
3. Vasodilator nerves—via posterior roots—centers in postroot ganglia.
4. Heat locally which may liberate acetylcholine.

(B) Vasoconstrictors:

1. Pressor substances—adrenalin, pituitrin, and unknown physico-chemical substances.
2. Sympathetic nervous system.
3. Cold locally.

Both effects, whether of constriction or relaxation, are controlled through the vasomotor center. Reflex afferent impulses to the brain such as pain, heat, cold, and traumatic shock will modify the tone of the capillaries. The central effect of the emotions may produce blushing or pallor of the skin. All these physiologic effects act to modify the circulation in the legs and arms as well as the vascular supply of the viscera. The major clinical effects, however, are brought about by one of two conditions—abnormal vasomotor effects on the capillary bed or organic changes in the vascular walls. In other words, in clinical practice we must differentiate between functional and organic disturbances.

At the bedside it is necessary, of course, to employ simple diagnostic measures. A careful history should be elicited, attention being directed to the general health of the patient, previous illness, and a story of the vascular disturbance from its earliest beginning. It must be determined whether there is pain, numbness, burning, or a sensation of cold. Is the pain made worse with exercise or exposure of the extremities to low temperature? Is there a change in the color of the skin when the leg is raised or lowered? These and many other features of the case can be learned by careful questioning. In the physical

examination the state of the general circulation must be determined—the blood pressure, pulse pressure, pulse rate, edema, cyanosis, air hunger. The lungs and the digestive and nervous systems should be carefully checked over. Much valuable data can be elicited by simple inspection and palpation of the affected parts. The diseased leg can be compared with the normal extremity. As a general rule an accurate diagnosis can be established without the use of instruments of precision; however, in difficult or severe cases it may be advisable to refer the patient to the vascular service of a large hospital or clinic.

DIAGNOSTIC MEASURES

(A) *Inspection of the Extremities—Patient in Supine Position.*—1. When pallor is present, the superficial blood vessels are either empty or only partially filled. If a moderate pallor becomes more marked when the leg is raised from a horizontal position to a level slightly above that of the heart, it is probable that structural impairment of the circulation is present. In instances of deficient blood flow in the arterioles, the pallor is associated with coldness, and cyanosis may appear when the leg is placed in a dependent position.

2. Redness of the extremity indicates that the superficial capillaries are dilated. If this is associated with coldness of the skin the capillary stasis is intensified by diminished inflow of blood, while if the skin is both red and warm there is increased minute volume flow through the dilated vascular bed.

3. Cyanosis of the skin is produced by an insufficient supply of oxygen in the cutaneous vessels. If the cyanosis fails to disappear following the local application of heat, there is probably organic obstruction in the arterioles.

4. Ulceration is produced by impaired arterial flow. When the ulcer remains indolent, there is the added factor of infection.

5. Gangrene of the extremity results from prolonged anoxemia. In such instances, the arterial supply has been obstructed and collateral circulation is absent or insufficient to maintain viability of the part.

6. In disease conditions of the vascular supply to the leg or arm, one often observes a change in color of the skin when

the extremity hangs in a dependent position. Increased redness indicates dilatation of the superficial vessels with no marked impairment in minute volume blood flow. If the lowered limb becomes cyanotic, there is stasis in toneless blood vessels. And finally if there is both redness and cyanosis, the vessels of the skin are dilated but the stasis is less severe. However, the oxygen supply is still deficient in quantity.

(B) *Palpation*.—By palpatory methods, it can be determined whether the arterial pulsations are present in the dorsalis pedis, posterior tibial, femoral, radial, brachial, and axillary vessels. Likewise, the temperatures of the contralateral arm or leg can be compared with that of the affected extremity. This observation should be made in a warm room, preferably at about 80° F. Beginning with the larger artery, the pulsation can be traced distally until the pulse becomes imperceptible. In the smaller arteries the accessibility of the pulsation is modified by the amount and character of the surrounding tissues. These vessels often take an abnormal course or they may be absent in conditions of health. Reich² has shown that, in normal people, the dorsalis pedis pulsation is absent in 4 per cent and abnormally placed in 8 per cent of patients. Under similar circumstances the posterior tibial artery is absent in 5 per cent. It must be noted, however, that absent pulsation is not inconsistent with a proper oxygen supply to the peripheral tissues.

These simple methods of inspection and palpation, when correlated with the general condition of the patient, will reveal a great deal about the dynamics of the peripheral circulation. In those more difficult or severe cases that are sent to the hospital for study, more elaborate methods of procedure are available. These tests pertain particularly to prognosis and treatment. It must be determined whether the disease is vasospastic or organic and whether the problem can be best handled by medical or surgical therapy. It must be known, for instance, whether the peripheral blood vessels can relax at all and, if so, to what extent. In cases of gangrene the point at which efficient circulation ceases must be determined. These problems are often difficult to solve. Several available measures, while valuable, require the services of an experienced observer.

1. Surface temperature readings by the electric thermocouple. This method registers by its effect on electric potential the influence of changes in temperature of the skin of the extremity. One reading is of no great value, so the test must be repeated on several different days. In making the test, a room should be used in which the temperature is constant and at the same level each time. The gradient of temperature change is determined at various points from the proximal to the distal portions of the extremity. A comparison is then made with the readings on the normal side which also are taken under the same conditions. Any marked difference on the two sides or any sudden decrease in temperature as one progresses distally suggests impaired circulation. In our experience we have usually been able to detect significant changes in temperature by simple palpation with the hand. The thermocouple readings can be used as a check method.

2. A second local method of investigation is to determine the degree of vasodilatation in the skin. Histamine, in the dose of 0.1 cc. of 1:1000 solution, is injected intracutaneously. A wheal of edema and a flare of capillary dilatation should appear within five minutes and attain a minimum degree of redness and size. This visible reaction gives us some idea of the available flow to the skin and some conception of the efficiency of collateral circulation. It is frequently used as an aid to localize the optimum level for amputation.

3. Three methods of great value are available to determine whether the peripheral vascular disease is due to organic vascular obstruction or due, in a greater or lesser degree, to vasoconstriction.

(a) Spinal anesthesia. This procedure effectively removes the tonus of the sympathetic nerve to the vessels in the lower extremities. If the disease is due to vasospasm, there is increased redness and heat in both the affected and sound leg when anesthesia to pain is established. General anesthesia, on the other hand, gives similar effects in all four extremities.

(b) Peripheral nerve block by the injection of a local anesthetic into a peripheral nerve trunk has served to release the sympathetic as well as the somatic nerve control to the distal area. The technique of this test is given in the excellent publication of Morton and Scott.³

(c) Probably the most satisfactory test is the determination of the effect on the peripheral circulation of an increase in the internal production of heat. Under normal conditions, when fever is produced by natural or artificial means, there is a reflex dilatation of the peripheral arterioles and capillaries. The investigations of the late George Brown⁴ have demonstrated conclusively that the peripheral arterioles and capillaries relax during typhoid hyperpyrexia. Furthermore, he found that the relaxation of spastic vessels may be equally valuable from a therapeutic standpoint inasmuch as the circulation may be distinctly better for a considerable period of time following this treatment.

4. Arteriography is a fourth method of study. When thorium dioxide is injected into the main artery of the affected extremity, proximal to the area of impaired circulation, details of the arterial and capillary circulation can be visualized on x-ray plates. This method may serve to differentiate between thrombo-angiitis obliterans and arteriosclerosis. In the former, there is increased capillary circulation while in the latter the anastomotic channels are limited in number. This method of diagnosis is of little value to one who has not had considerable experience with the interpretation of roentgenograms.

The recognized diseases of the peripheral vascular system may be divided into organic and vasospastic. For the purpose of convenience and brevity, an outline has been made of the principal points in those diseases which are commonly seen in daily practice.

ORGANIC LESIONS

(A) *Thrombo-angiitis obliterans.*

1. A disease of active maturity.
2. More common in men.
3. Most frequently observed in Hebrews.
4. Commonly associated with the excessive use of tobacco.
5. Pallor of extremity when elevated 90 to 180 degrees.
6. Flushing of the dependent limb.
7. Diminished pulsation in the arteries of the feet.
8. Pallor of foot on passive motion.
9. Migrating phlebitis in from 20 to 25 per cent of cases.
10. Associated scleroderma (occasionally).
11. Trophic changes, *i. e.*, superficial blebs, desquamation.
12. Arteries seldom visualized by plain roentgenograms.
13. Increased collateral circulation by arteriography.

(B) *Arteriosclerotic gangrene.*

1. Cardiac hypertrophy, hypertension, palpable thickening of arteries, accentuated aortic second sound.
2. Arteriosclerosis of fundus and conjunctival vessels.
3. Calcification of larger arteries as demonstrated by roentgenograms.
4. Absence of arterial pulsations in feet (not diagnostic).
5. Coldness of extremity.
6. Pallor and cyanosis of limb.
7. Gangrene—trauma plus infection.

Symptoms Suggestive But Not Diagnostic of Arteriosclerotic Gangrene

1. Increasing intolerance of extremities to cold.
2. Acroparesthesia.
3. Muscular fatigue.
4. Aching pains.
5. Nocturnal cramps and hot feet.
6. Intermittent claudication.

(C) *Arterial embolism.*

Predisposing factors.

1. Rheumatic heart disease.
2. Bacterial endocarditis.
3. Auricular fibrillation.
4. Mural thrombi after coronary occlusion.

Symptoms.

1. Extreme pain at site of embolus one and two hours after obstruction of vessel. Pain spread peripherally.
2. Waxy pallor locally.
3. Dark blue cyanosis distally.
4. Proximal blotchy discoloration.
5. Coldness distally.
6. Decreased cutaneous sensibility.
7. Reduced reflexes in affected limb.
8. Paralysis in certain cases.
9. Gangrene if collateral circulation is deficient.

(D) *Latent phlebitis.*

This condition, which is very common, may follow local trauma, burns, and local and focal infections. It is bacterial in origin.

Symptoms.

1. Aching and pains in the extremities involved.
2. Early fatigue of affected parts.
3. Cramps in muscles.
4. Sense of undue heat.
5. Local itching and eczema.
6. Deep veins sensitive to pressure.
7. Variations of symptoms with barometric pressure changes.

Other conditions which are encountered less commonly are venous thrombosis in the axillary vein induced by effort, periarteritis nodosa, and specific and nonspecific arteritis.

FUNCTIONAL VASOSPASTIC DISEASES

(A) *Raynaud's disease.*

Stages.

1. Arterial spasm, white syncope, local asphyxia.
2. Capillary dilatation (reflex—cyanotic asphyxial stage).
3. Arterial relaxation—warm red stage.

Diagnostic criteria (Allen and Brown⁵).

1. Intermittent attacks of discoloration of distal parts.
2. Symmetrical, bilateral involvement.
3. Absence of clinical evidence of occlusive disease of the peripheral arteries.
4. Gangrene and trophic changes limited largely to the skin; may be associated with scleroderma.
5. Absence of primary organic disease.
6. Predilection for women.

(B) *Erythromelalgia* (Weir Mitchell's disease).

Characteristic features.

1. Bilateral burning pains, often in intermittent attacks.
2. Sudden increase in redness, flushing or congestion, and increase in temperature of dependent limb.
3. Production and aggravation of the distress by heat and exercise.
4. Relief of discomfort by means of rest, elevation or the application of cold to the affected extremity.
5. Bilateral distribution of the disease.

(C) *Acrocyanosis.*

This condition occurs quite commonly in young people—often at puberty—and in those who have unstable sympathetic nervous systems. Symptoms of an endocrine disturbance may be associated with it and it often is a part of the syndrome of neurocirculatory asthenia. There is sweating and coldness of the hands and feet; the sweating is profuse and some puffing in the affected areas occurs. The symptoms are increased by exposure to cold or by psychic stimulations.

Secondary vascular spasms may occur in a variety of different conditions which produce sympathetic irritation. These include:

1. Neurologic conditions, such as poliomyelitis, multiple sclerosis, amyotrophic lateral sclerosis, syringomyelia, hemiplegia in late stages, and spina bifida.
2. After trauma such as strains, contusions, and fractures.
3. In certain cases of cervical rib.
4. Following the prolonged use of a pneumatic hammer. As a rule, such vascular disturbances are not difficult to diagnose if we will but think of all the possibilities in each case.

TREATMENT

Scupham and De Takáts⁶ have in a very excellent review brought the treatment of peripheral vascular disease up-to-date. In this comprehensive article, therapy is divided into medical and surgical procedures. The former include specific and general measures, the use of drugs, biologic products, and passive vascular exercise. Surgical measures include efforts to improve impaired circulation, to alleviate pain, and to remove nonviable parts at an optimal time and at an optimal level. Only a summary of those measures which are of a practical value can be presented here. Further details may be found in the original article.

MEDICAL THERAPY

(A) Specific measures.

1. If polycythemia vera is the underlying cause, acetylphenylhydrazine or roentgen therapy may be used.
2. In associated hypothyroidism, the proper dose of thyroid extract is necessary.
3. Syphilis requires adequate antiluetic therapy.
4. Congestive heart failure necessitates rest, digitalis, and often mercurial diuretics.

(B) Foci of infection.

1. Acute and chronic foci of infection must be eliminated by the use of proper measures.

(C) Measures to avoid amputation of the affected arm or leg.

1. Keep the entire body warm.
2. Protect the feet from trauma, chilling, and infections.
3. Use the temperature foot cradle (optimum temperature for the relief of pain is 33°–35° C.).
4. Use contrast baths.
5. Keep the position of the limb at the level of greatest circulatory efficiency, usually 10° to 15° below the horizontal position.

(D) General measures.

1. Bed rest.
2. Prohibit all use of tobacco in all instances of peripheral vascular disease.
3. Artificial fever (typhoid), especially in Buerger's disease.
4. Intravenous saline solution, 5 per cent, in mild cases of Buerger's disease.

(E) Tissue extracts intramuscularly may be tried for the relief of intermittent claudication. Insulin-free pancreatic extracts are best, but extracts of skeletal muscle have been used.

Apparently, as the result of such injections, there is increased ability of the muscles to do work with the available blood supply. Many patients do well with 1 injection a week.

(F) Drugs. 1. Alcohol, in doses of 0.5 cc. per kilogram of body weight, produces vasodilatation in short periods. It is valuable for relief of pain in arteriosclerosis with occlusion, and it may reduce the severity of a chill after the use of intravenous typhoid therapy.

2. Compounds of theobromine are of value in aiding prolonged vasodilatation, especially in arteriosclerosis. Theophylline ethylenediamine produces similar effects.

3. Papaverine has been employed in sudden arterial occlusion (Denk). It is given intravenously every two or three hours for several days if necessary. It should relieve the symptoms after 2 injections, if at all. Apparently, the benefit is due to relief of widespread arterial spasm.

(G) Passive vascular exercise (pavex). Alternate positive and negative pressure is applied to an extremity.

1. Landis and Gibbon⁷ employ an aluminum box with the extremity sealed in a rubber cup. Suction is used at 120 mm. of mercury for twenty-five seconds and pressure is maintained at 80 mm. of mercury for five seconds.

2. Hermann and Reid⁸ have devised a glass boot. In this, suction is limited to 80 mm. of mercury and pressure to 20 mm. of mercury. If the response is satisfactory, a rise in cutaneous temperature appears in all patients who are treated two weeks or more. All evidence of pain disappeared in 86 per cent of the patients, and the pain of ischemia has been gradually relieved except in severe gangrene. Small changes of pressure should be used at first. Acute infection and venous thrombosis are a contraindication for this therapy. The results are most satisfactory in cases where only the smaller vessels are involved.

Recent work has produced disappointing results in the use of passive vascular exercises. More satisfactory end-results are obtained when the venous pressure is increased by the use of a pressure cuff about the muscles of the extremity which was originally described as Bier's passive hyperemia. J. R. Smith⁹ has employed a combination of increased venous pressure with intravenous injections of hypertonic saline solution. His results have been superior to those following pavex therapy.

SURGICAL THERAPY

Recently, there has been a conservative attitude toward surgical treatment. This is largely due to: (1) the earlier recognition of disease of the peripheral circulation; (2) a more thorough understanding of etiology; and (3) a better understanding of natural methods of compensation for circulatory disorders.

Three surgical procedures are in use which are designed:

(A) To improve impaired circulation.

1. Ligation of a vein has been used especially in arteriosclerosis and thrombo-angiitis obliterans. There is no sound physiologic basis for this procedure. Better results have been observed in acute rather than in chronic obstruction. When favorable results occur, there is increased systolic pressure, increased venous pressure, diminished volume flow of blood, increased surface and deep temperature, increased collateral circulating bed, and the diminished incidence of gangrene. However, in most cases there is no definite or proved benefit.

2. Arterial ligation may be done to stimulate collateral circulation, especially in Buerger's disease. As a rule it is not successful.

3. Arterial excision (arteriectomy) is presumed to interrupt reflex vasoconstriction. This also is not entirely successful.

4. Periarterial sympathectomy (Leriche) consists in the removal of sympathetic nerve fibers from the veins and main nutrient artery. The hyperemia which results appears to be evanescent.

5. Sympathetic ramisection consists of interruption of the gray rami connecting the ganglionated trunk with the peripheral nerves. Objections to this procedure are that: (1) it is difficult to distinguish all anatomic variations, and (2) the posterior ganglion fibers readily regenerate.

6. Sympathetic ganglionectomy is preferred. In the upper extremity, it is necessary to cut the dorsal sympathetic trunks below the second dorsal ganglion. For the lower extremity, the second, third, and fourth lumbar ganglia must be removed.

(B) To alleviate pain.

1. Peripheral nerve block by use of alcohol, sectioning, and crushing.

2. Paravertebral block which is used in elderly patients.
3. Intraspinal injection of alcohol.
4. Chordotomy (spinothalamic tracts).

(C) To remove nonviable parts, especially in arteriosclerosis and diabetic gangrene.

The site of amputation is determined by the skin temperature and the reaction to histamine. These usually indicate the same level of circulatory efficiency.

CONCLUSIONS

1. Under ordinary circumstances the diagnosis of peripheral vascular disease is not difficult at the bedside.

2. The important procedures consist of a careful history, complete clinical examination of the cardiovascular, pulmonary, and venous systems, and local examination of the extremities by inspection, palpation and postural changes.

3. Hospital care is indicated in severe or difficult cases when special diagnostic or therapeutic procedures are necessary.

4. As far as possible, treatment should be conservative. When medical measures fail, surgical therapy may be instituted to improve the local circulation, to alleviate pain, and to remove devitalized parts.

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THE CLINICAL SIGNIFICANCE OF PRECORDIAL PAIN

A. CARLTON ERNSTENE

THE attachment of grave significance to symptoms of minor importance may be quite as detrimental to a patient's welfare as the improper interpretation of symptoms of serious organic disease. The truth of this statement is nowhere better illustrated than by the problem of evaluating precordial pain. To the laity, heart pain has become synonymous with liability to sudden death, and every practitioner is familiar with the patient who comes apprehensively for advice concerning pain in the precordial area. To attribute this pain erroneously to organic heart disease may result in the development of a severe anxiety neurosis and even semi-invalidism. On the other hand, an error in which pain of cardiac origin is not recognized as such may result in the premature death of the patient. Fortunately, it is not often difficult to distinguish between true cardiac pain and precordial pain due to noncardiac causes, but at times a correct decision can be made only after a most careful study.

Pain in the precordial area occurs much more commonly in the absence of organic heart disease than in association with it. The most common form of true cardiac pain is that of angina pectoris but this pain almost always originates in the substernal region and not in the precordial area. The pain or oppression may radiate to the precordium, however, and rather infrequently it may even have its initial location there. In the latter instances, there is almost always prompt radiation to the substernal region. This feature is of great assistance in distinguishing the pain of angina pectoris from less important types of precordial discomfort, for while other forms of precordial pain may at times radiate to the left shoulder and even down the left arm, radiation to the substernal region practically

never occurs. It is also important to remember that, in its characteristic form, the pain of angina pectoris is of short duration and is relieved promptly by the administration of nitroglycerin.

The most common form of precordial pain is not in any way related causally to organic heart disease although it is not uncommon in patients who have myocardial or valvular lesions. This pain is described by the patient as dull or aching in character or merely as a sense of heaviness. Associated with it there may be occasional or frequent twinges of sharp, sticking pain. Careful questioning usually elicits the information that fatigue and emotional stress are the two most important predisposing factors but the pain may be precipitated or made worse by exertion. Usually the discomfort remains sharply localized to the lower or upper precordium but in exceptional cases it may radiate to the left shoulder or left arm. It is seldom sufficiently severe to cause the patient to stop the activity in which he is engaged at the time, and rest gives only gradual relief. In contrast to the oppression of angina pectoris, the pain frequently lasts for two or three hours at a time and may even persist for a day or more without interruption. Nitroglycerin gives little or no relief. Physical examination frequently reveals the presence of tenderness over the precordium, a finding that is uncommon in patients with uncomplicated organic heart disease.

The most common cause of dull, aching precordial pain is neurocirculatory asthenia. This is a condition characterized principally by dyspnea and palpitation on limited exertion, weakness, fatigue, nervousness and tremulousness, in addition to the precordial discomfort. The symptoms usually develop for the first time during adolescence or early adult years and often appear to be causally related to some unusual exertion, to an acute infection such as influenza, or to a period of prolonged nervous strain. Physical examination shows evidence of an unstable sympathetic nervous system. Flushing of the face, neck, and upper chest is frequently present, the hands and feet are cool and clammy, and there is profuse sweating in the axillae. Sighing respiration is common. The heart is not enlarged but the apex impulse is forcible and systolic murmurs are often heard over the base or apex. Sinus arrhythmia

usually is present. Moderate exertion causes an undue rise in the respiratory and heart rate and, after completion of the exercise, the return to the resting level is delayed beyond the normal.

Dull, aching, precordial pain of the type encountered in patients with neurocirculatory asthenia may occur in women as a part of the menopausal syndrome and is a not infrequent complaint of individuals with essential hypertension but without evidence of organic heart disease. Patients who have organic heart disease may have neurocirculatory asthenia as well, and in these cases it often is difficult to determine the degree to which the latter condition rather than valvular or myocardial disease is responsible for the individual's symptoms. The differentiation is, of course, extremely important not only because of its bearing on prognosis but also because a frank explanation of the mechanism of the symptoms is often helpful in allaying the apprehension of the patient. It is important to remember in problems of this kind that, with the exception of occasional cases of angina pectoris and a few conditions to be discussed later, organic heart disease does not cause precordial pain. Even congestive heart failure does not produce pain of this kind although it may be attended by a rather widespread sense of heaviness within the chest. In the patient with neurocirculatory asthenia and organic heart disease, there usually is a striking discrepancy between the principal symptoms, such as dyspnea, palpitation and exhaustion, and the degree of disability one might reasonably expect from the physical findings. Furthermore, the response of the symptoms to treatment usually is much less satisfactory than in many patients with mild or even moderately severe congestive heart failure.

Precordial pain of a dull or aching character may result from paroxysmal tachycardia or from any sustained elevation of the heart rate in a hypersensitive patient. There is no evidence that this pain is in any way indicative of myocardial fatigue. Paroxysmal tachycardia may also cause substernal oppression of the type characteristic of angina pectoris. This pain is much more severe than the dull precordial ache and frequently radiates in the manner of typical anginal pain.

Acute fibrinous pericarditis occasionally produces precordial pain which may amount only to fleeting but repeated

twinges of sticking pain or to a sense of heaviness, or may be excruciatingly severe and boring or cutting in quality. Usually, however, pericarditis is not attended by pain of any kind. Precordial discomfort or sticking pain not infrequently is a complaint of patients who have acute rheumatic fever, and there is evidence that the incidence of permanent cardiac damage is greater in these individuals than it is in patients who have no such discomfort. Occasionally in high-strung persons, momentary sharp or sticking precordial pain may accompany premature beats or the forceful ventricular contraction which follows a premature beat.

The most severe form of cardiac pain is due to acute coronary artery occlusion and, except for its greater intensity and longer duration, is similar to the pain of angina pectoris. As in the case of angina pectoris, the pain usually originates in the substernal area and seldom in the precordium although it often spreads to involve this region. The other features of the condition such as the shock, fever, leukocytosis, pericardial friction rub and the electrocardiographic changes have been described too frequently to warrant repetition at this time.

Infarction of the lung secondary to pulmonary embolism may, when suitably situated, cause pain in the region of the left breast due to the development of fibrinous pleurisy over the infarcted area. The relationship between the pain and the respiratory movements and the presence of a pleural friction rub are the most helpful diagnostic features. Sudden occlusion of a large pulmonary artery characteristically causes severe dyspnea with substernal oppression and the rapid development of a state of shock. The clinical picture may closely simulate that of coronary thrombosis. Pulmonary embolism of this severity causes prompt dilatation and failure of the chambers of the right side of the heart and this in turn gives rise to certain physical signs which are of great value in diagnosis. Chief among these are an increased pulsation palpable in the second left interspace adjacent to the sternum, accentuation of the pulmonary second sound, the frequent occurrence of a gallop rhythm over the pulmonary area, and the occasional presence of a friction rub in the second, third, and fourth interspaces adjacent to the sternum.¹ Dissecting aneurysm of the aorta also gives rise to a symptom complex which closely

resembles that of coronary occlusion. The condition is characterized by the sudden onset of severe pain in the anterior chest, often radiating to the back and legs, and usually described by the patient as crushing or tearing in quality. The pain usually lasts for forty-eight hours or longer and frequently is present to a greater or lesser degree until death occurs. In contrast to coronary artery occlusion, however, the blood pressure remains elevated and there is no diminution in the quality of the heart sounds. Electrocardiograms show no coronary T-wave changes.

Aneurysm of the aorta may cause pain in the substernal or precordial region by pressure upon the sternum, ribs, or nerves. Luetic aortitis without aneurysmal dilatation usually causes no pain except in patients in whom aortic insufficiency, partial occlusion of the coronary orifices, or sclerosis of the coronary arteries is responsible for the occurrence of angina pectoris. Occasionally, however, there may be a complaint of more or less constant vague pain in the upper substernal region which is not appreciably affected by exertion.

Arthritic changes in the spine and, less commonly, infectious processes in a chondrosternal joint may occasionally cause severe pain in the precordial area. In the former case, the pain usually is directly related to movements of the spine or to use of the arms and frequently is not affected by such forms of exertion as walking; while in the latter, there is usually tell-tale tenderness with or without local swelling over the involved chondrosternal joint.

Finally, mention should be made of the fact that many individuals with functional disturbances of the colon complain of dull pain or a sense of pressure over the lower precordium or in the left subcostal area. The discomfort is not related in any way to exertion, and a thorough history usually enables one to evaluate the symptom correctly.

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DIAGNOSIS AND TREATMENT OF CEREBRAL VASCULAR ACCIDENTS IN ARTERIOSCLEROSIS

R. H. McDONALD

CEREBRAL HEMORRHAGE is undoubtedly the most common and most dramatic accident which may accompany cerebral arteriosclerosis. It is practically always arterial in origin. Venous hemorrhage is usually traumatic or associated with conditions which suddenly increase venous pressure. Capillary hemorrhage is usually associated with toxic processes or with acute inflammatory disease, for instance, encephalitis. Intracranial arterial bleeding may be extradural, subdural, or subarachnoid or intracerebral. The first three are likely to be the result of trauma.

The most common cause of intracerebral arterial hemorrhage is rupture of an atheromatous artery in an individual suffering from hypertension. The increase in blood pressure is usually due to an essential hypertension, much less frequently chronic nephritis, or any of the other causes of increased blood pressure. The two essential components in the production of hemorrhage are therefore a degenerated artery and an increased strain upon it. The arterial degeneration is, of course, produced by the increased blood pressure over a period of time. An increased strain upon the arterial wall produces hypertrophy of the media which eventually undergoes some degeneration and an atheroma of the intima occurs as a result partly of the raised pressure and partly of the degeneration. The end-result is a somewhat thickened vessel which has, however, suffered considerably in the loss of its elasticity. Hemorrhage does not occur in the presence of hypertension alone unless there is accompanying vascular deterioration, and vascular deterioration in the absence of hypertension is more likely to lead to thrombotic accidents than to actual hemorrhage. Cerebral hemorrhage is thus comparatively rare in

younger hyperpietics and is much commoner in late middle life, males being more commonly affected than females. A tremendous familial incidence is commonly seen.

Certain premonitory signs of beginning cerebral vascular degeneration which may presage the onset of hemorrhage may be noted in hyperpietics. The onset of cerebral sclerosis is often so insidious and gradual that it escapes the clinician's notice. Involvement of the cerebral cortex in milder cases results in some general reduction in intellectual capacity with impairment of memory, especially for recent events, and a tendency to increased emotional reaction. The tendency to reminiscence is well-known. Depression is not uncommon and there may be attacks of confusion leading at times to rather poorly defined delusions, often of the paranoid type. Localization of vascular changes in the motor area may lead to the development of petit mal, jacksonian attacks, or even of generalized epileptic fits. Various forms of aphasia and apraxia may be seen. There may be involvement of the pyramidal tract. A senile tremor is common and may be associated with an arteriosclerotic parkinsonism. Various types of visual disturbances may be noted. In individuals manifesting such evidences of cerebral vascular degeneration, the existence of a hypertension suggests strongly the possibility of the development of a frank cerebral hemorrhage.

In most cases, the actual onset of hemorrhage is sudden and is associated with factors which suddenly elevate the blood pressure to some degree, such as emotion, exercise, or defecation. However, it is well known that many of these develop during rest and while the patient is asleep. The patient usually complains of sudden, severe headache and he may be nauseated. There is a feeling of confusion. The patient complains of being dazed and in the great majority of cases loses consciousness in a few minutes. Occasionally there may be a convulsion at the onset of unconsciousness. The duration of the unconscious period is extremely variable, depending upon the degree and severity of hemorrhage and is an important point in determining the prognosis.

One of the most common locations for the occurrence of hemorrhage is in the lenticulostriate artery supplying the internal capsule on one or the other side. In the presence of

such an accident unconsciousness develops quickly, the depth of coma depending upon the size of the hemorrhage and the degree of shock. A slight degree of fever is usually present, the respirations are deep and stertorous, and respiratory irregularities, for example, Cheyne-Stokes respiration, may occur. Bradycardia is common, the pulse rate averaging 50 or 60 and being full and bounding. The head is usually rotated, the eyes deviating toward the side of the lesion. This is due to paralysis of rotation of the head and of conjugate deviation of the eyes to the opposite side and the consequent unbalanced action of the undamaged cerebral hemisphere. Some inequality of the pupils may be noted; the pupillary reaction to light is still present unless very deep coma has supervened. A divergent squint is common. The corneal reflex is often lost on the side opposite to the lesion and on both sides when the coma is more marked. Ophthalmoscopic examination may reveal slight edema of the disk if there is increased intracranial pressure, and usually definite signs of retinal arteriosclerosis will be noted.

The hemiplegia caused by interruption of the pyramidal fibers by a capsular lesion is on the side opposite to the lesion and in the unconscious patient this may be determined by observation and tests. It will be noted that the nasolabial furrow is flattened on the paralyzed side and that the cheek is puffed out more markedly on that side during expiration. The paralyzed limbs will be found to be flaccid and, if lifted up, will fall to the bed inertly, whereas even in deep coma the normal arm and leg subside much more gradually. Painful stimuli may be used to demonstrate the presence of paralysis in patients who are not too deeply comatose. However, it must be remembered that the absence of protective movement on the application of pinprick may be due to hemi-analgesia. The tendon reflexes on the paralyzed side are usually much diminished or entirely absent although they may even be exaggerated. The plantar reflex on the affected side is extensor. The abdominal reflexes are often lost on both sides. Retention or incontinence of urine and feces are the rule as long as the patient is unconscious.

When the patient suffers hemorrhage in the area of the pons, there is a facial paralysis on the side of the lesion with

a flaccid paralysis of the limbs on the opposite side. The patient lies with the head and eyes turned toward the side of the paralyzed limb if the lesion is unilateral. Frequently, lesions of the pons become bilateral in a short period of time, giving rise to a flaccid paralysis of the limbs on both sides with bilateral extensor plantar reflex. Pontine hemorrhage is frequently associated with a disturbance of the heat-regulating centers in the hypothalamus and hyperpyrexia develops, particularly in the presence of the usual effort to keep the patient warm. Extreme myosis as the result of the bilateral destruction of the ocular sympathetic fibers is characteristic of pontine hemorrhage.

Rupture of a hemorrhage into the lateral ventricle usually precipitates a deep coma of sudden onset with evidences of a lesion of the pyramidal tract on both sides of the body. A posture of rigid extension is frequently adopted and the hyperpyrexia so characteristic of pontine hemorrhage may develop.

The development of a massive cerebral cortical hemorrhage produces focal symptoms dependent upon the location. In the frontal area, the most characteristic localizing symptom is a motor aphasia due to a disturbance of the cortical cells of the posterior part of the third frontal convolution (Broca's area) and the lower part of the precentral convolution. It is conceivable that a focal hemorrhage in the frontal lobe in such a position as to press upon the olfactory nerve would lead to anosmia on the side of the lesion. Impairment of memory and reduction of intellectual capacity are common evidences of a lesion of the frontal lobe and may be accompanied by marked changes in personality and increased irritability.

Focal hemorrhages in the precentral gyrus will characteristically give rise to an excitation of the cortical motor area with resulting jacksonian attacks, frequently without loss of consciousness. With further destruction of the cortical cells, motor weakness on the opposite side of the body results and exhibits a regional distribution corresponding to the representation of parts of the body in the precentral convolution.

Lesions in the anterior portion of the temporal lobe involving the uncinate gyrus cause a marked disturbance of the function of tasting and smelling and because of irritation may result in the so-called "uncinate fits" which are characterized

by hallucinations of taste and smell and short periods in which the patient loses contact with his surroundings, often accompanied by involuntary tasting or licking movements. Complete destruction of the cortical cells in this area leads to an impairment of taste and smell. Lesions involving the post-central convolution of the parietal lobe particularly give rise to irritation of the motor sensory nerve with paresthesias referred to the opposite side of body—so-called “sensory jacksonian attacks.” These begin in that part of the opposite side of the body corresponding to the focus of excitation, frequently spread to other parts of the sensory area, and may be followed by motor discharge. Destruction of the cortical cells in this area results in a loss of the finer discriminations of sensation whereas the crude appreciation of pain and thermal sense is left intact.

Hemorrhages involving the occipital lobes frequently give rise to a lessening of acuity of vision and defect of the visual fields, recognition of which is of extreme importance in localizing the lesion.

In general, these cortical manifestations of cerebral hemorrhage are much less well defined than in the case of cerebral neoplasms. This is due to a tendency of the hemorrhage to spread over the cortical region and also because of the frequently associated cortical changes elsewhere.

The diagnosis of cerebral hemorrhage is usually made relatively easily from the history and physical examination alone. Albuminuria is present in most instances and, as a result of the cerebral trauma or shock, glycosuria is frequently seen. Examination of the cerebrospinal fluid may yield some information. It is usually under somewhat increased pressure and its protein content is elevated to some degree. Blood cells may be found in the fluid when the hemorrhage has ruptured either into the ventricular system or into the subarachnoid space.

Cerebral hemorrhage may be simulated somewhat closely by cerebral thrombosis, embolism, or subarachnoid hemorrhage. In cerebral thrombosis, the onset is usually much more gradual, the symptoms increasing in severity over periods of twenty-four to forty-eight hours. The coma is generally less pronounced and it is associated with conditions causing disease of the cerebral arteries leading to a reduction of their lumen

and intimal thickening as well as to factors causing increased coagulability of the blood and reduction of the circulatory rate. Cerebral thrombosis is seen in late middle life and old age and is associated with marked atheroma of the decrescent type unaccompanied by an elevation of blood pressure. In early middle life, a syphilitic endarteritis is the commonest cause and in young individuals it may accompany acute infections, severe anemia, or polycythemia. Since the pathologic condition develops gradually, the resulting symptoms may not reach their height for one or two days. Convulsions are relatively common. The end-result is a focal scarring, depending upon the vessel affected.

Cerebral embolism is more sudden and more dramatic in its onset than cerebral hemorrhage and is associated with the presence of some surgical operative field or area of thrombosis elsewhere in the body, although this latter may be obscure. After the initial attack, the symptoms may increase in severity over a period of time as a result of secondary cerebral edema and thrombosis.

Subarachnoid hemorrhage from a ruptured intracranial aneurysm occurs usually at an earlier age than cerebral hemorrhage, frequently in young adults without any antecedent symptoms whatever. Meningeal irritation constitutes a prominent symptom and blood in the spinal fluid is regularly observed. There may be focal signs of destruction of cortical tissue but lesions of the pyramidal tract are seldom seen, and coma is much less profound than in cerebral hemorrhage.

When a patient is seen in a stage of coma, various other causes for such a state must be kept in mind. Coma associated with intracranial neoplasms is usually accompanied by marked evidences of increase in the intracranial pressure. Hemorrhage into a degenerating cerebral tumor may give rise to a gradually developing coma and, if this is associated with hypertension in an elderly adult, the differential diagnosis may be difficult. The history of injury will differentiate most cases of coma secondary to cerebral trauma. Coma following an epileptic convulsion is usually of short duration unless there has been a succession of attacks. Diabetic comas can be recognized by the increased rate and amplitude of the respirations and the decreased ocular tension as well as by the characteristic

urinary findings of acetonuria, glycosuria, and increased blood sugar. Hypoglycemic coma is characterized by an abnormally low blood sugar due to excessive dosage of insulin or rarely by a tumor composed of the cells of the island of Langerhans of the pancreas. Uremic coma, particularly in chronic hemorrhagic Bright's disease, may cause some difficulty in differential diagnosis of cerebral hemorrhage in view of the increased blood pressure which is common. If a history of nephritis is obtainable, it is of course of great value. A physical examination reveals the presence of an albuminuric retinitis and examination of the urine shows low specific gravity with albumin and casts. The examination of the blood shows an increased amount of nitrogenous metabolites, the blood urea rising to levels of more than 200 mg. per 100 cc. of blood. Coma associated with various types of intoxication must be considered although it rarely offers much difficulty in differential diagnosis. The chief drugs concerned are alcohol, various forms of opium, and other sedative drugs such as chloral and the various barbituric acid derivatives.

At the onset of cerebral hemorrhage, the prognosis as to life and disability is always difficult. Death may occur without recovery of consciousness due to increased intracranial pressure giving rise to medullary anemia, or because of malnutrition, exhaustion, or intercurrent infection. The presence of progressively deepening coma suggests the continuance of hemorrhage and evidences a bad prognosis. The pulse tends to become rapid and irregular, the respiratory rate becomes rapid, irregular, and shallow with an increasing temperature and blood pressure. Coma which persists for more than forty-eight hours is of very serious prognostic significance. Blood in the cerebrospinal fluid is usually of bad significance, suggesting an intraventricular hemorrhage.

With the recovery of consciousness, the question arises as to the degree of permanent disability. Some improvement is to be expected in practically all cases but rarely is there complete recovery. Some reduction of mental efficiency and of concentration and memory is frequently seen, together with an increased irritability and emotional instability. Aphasia associated with cortical hemorrhage in Broca's area usually recovers over a period of months, and the dysarthria accompany-

ing capsular hemorrhage frequently improves more rapidly. A spastic hemiplegia incident to damage of the pyramidal tract in internal capsular hemorrhage improves gradually, power returning to the lower limbs more readily. If there is no improvement at the end of three months, paralysis is likely to be permanent.

Usually some persisting sensory loss is associated with a lesion of the posterior part of the capsule, and pain in the paralyzed side of the body is not uncommon after capsular hemorrhage, usually being ascribed to an irritation of the optic thalamus. This is apt to be very persistent and troublesome. Tremors may develop in the affected limb, either on voluntary movement or when the limb is at rest. Trophic changes are common in paralyzed limbs and are evidenced by cyanosis and brittleness of the nails. In senile patients, an arthritis of the larger joints is commonly seen.

Surgical control of cerebral hemorrhage by ligation of the vessel is not practical in the case of intracerebral lesions. Our efforts, therefore, must be directed to reducing the hemorrhage as much as possible and lessening the increased intracranial pressure. It is desirable that the patient be moved as little as possible and that care be taken that nothing obstructs the venous return from the head. Cold applications to the cranium are generally advised. The removal of 500 cc. of blood by venesection is probably of distinct value in lowering the intracranial pressure, particularly in the plethoric type of individual, although it somewhat increases the chances of medullary anemia. The removal of spinal fluid by lumbar puncture will certainly lessen intracranial pressure but it is open to the objection that it may cause a compression of the medulla into the foramen magnum with resultant death. A reduction of the arterial blood supply to the head has been advised by compression of the internal carotid artery on the side of the hemorrhage, but this adds the danger of further cerebral impairment by further anemia of the hemisphere already anemic from compression due to hemorrhage. Purgation is usually advised in the unconscious patient by the time-honored method of applying 1 minim of croton oil in a little butter to the tongue. Further dehydration and consequent reduction of intracranial pressure may be secured by the rectal injection of

8 ounces of 25 per cent solution of magnesium sulfate. Regular catheterization will be necessary in the unconscious patient, and a regular intake of fluids must be arranged for either by the stomach tube or by infusion. The use of enemata and cathartics will frequently be necessary for a time after the patient recovers. Voluntary movements of the affected parts must be encouraged as soon as the immediate effects of the hemorrhage have passed. Massage and passive movements are of value in keeping up the local circulation and orthopedic appliances should be used to prevent contractures.

INDICATIONS FOR THE USE OF IODINE IN THE TREATMENT OF HYPERTHYROIDISM

GEORGE CRILE, JR.

INTRODUCTION

OVER 90 per cent of all malignant tumors of the thyroid, all large goiters, all intrathoracic goiters, and approximately one half of the cases of hyperthyroidism are the end-results of an iodine deficiency.¹ In all these conditions, the changes initiated by a deficiency of iodine in early life have resulted in the formation of adenomata with their attendant complications of hyperthyroidism, symptoms of pressure, or even malignancy. The widespread dissemination of this knowledge among both the medical profession and the public has led to sane legislation governing the addition of physiologic quantities of iodine to the table salt dispensed in areas of endemic goiter. As McClure² and Marine and Kimball³ and others have shown, the results of this action have been most satisfactory and the incidence of endemic goiter is steadily decreasing.

In spite of the progress that has been made in the prophylactic use of iodine, iodine is still employed in the treatment of established goiter where its use is clearly contraindicated. It is frequently given to patients with large adenomata without hyperthyroidism in the mistaken belief that the size of an adenoma can be diminished by iodine therapy. This practice is not only useless but is believed by some⁴ to be not devoid of the danger of inducing a state of hyperthyroidism. In view of the confusion which apparently still exists regarding the use of iodine, a résumé of its indications in the treatment of hyperthyroidism will be given.

THE PHYSIOLOGICAL ACTION OF IODINE IN THE TREATMENT OF HYPERTHYROIDISM

When a patient with a diffuse goiter with hyperthyroidism is given iodine, the hyperplastic gland fills with colloid, the

pulse rate falls, the basal metabolic rate is lowered, and a remission of the hyperthyroidism is induced.⁵

There has been much speculation and investigation as to the mechanism of this reaction, but all that is definitely known is that iodine exerts a direct action on the secretory mechanism of the thyroid gland so as to diminish its output of active thyroid hormone. This reaction appears within twenty-four hours after the administration of iodine and its maximum effect is noted from one to three weeks after the initiation of treatment. It is during this period that thyroidectomy can be performed with the maximum safety and the minimum reaction.

Much has been written regarding the phenomenon of "iodine escape." Many are of the opinion that iodine loses its effectiveness after a few weeks of continuous administration and that patients who take iodine over long periods of time become "iodine-fast" or "iodine-tolerant" so that the drug no longer exerts any control over the hyperthyroidism. It is true that in many cases the severity of the disease progresses in spite of the administration of iodine and that neither larger doses nor a continuation of the same doses of iodine will produce any further remission of its severity. Yet as Means and Lerman⁶ have shown, the hyperthyroidism in these so-called "iodine-fast" cases undergoes an exacerbation when iodine is withdrawn. This indicates that the continued administration of iodine exerts a continuous effect, perhaps more striking in the first few weeks, but nevertheless present so long as iodine is being given. The phenomenon of iodine escape (an exacerbation of the patient's symptoms while iodine is being given) is therefore not to be interpreted as the failure of iodine to exert a continuous depressant effect on the secretory activity of the thyroid but rather as an exacerbation of the disease itself which has occurred in spite of the iodine and would be more severe if the iodine were withdrawn.

In spite of the fact that many investigators have adopted the above point of view regarding the continuity of the action of iodine over long periods of time, there is little or no evidence to indicate that the administration of iodine will either cure a patient with hyperthyroidism or permanently modify the severity of the disease except as it depresses the secretory activity of the thyroid during the time it is given.

THE ADMINISTRATION OF IODINE BEFORE OPERATION IN PATIENTS WITH HYPERTHYROIDISM

It is of unquestionable advantage to the surgeon to see the patient with hyperthyroidism before iodine is given so that he may estimate the true severity of the disease and plan the time and the scope of the operation accordingly. This, however, is a minor consideration as compared with the unwise practice of treating hyperthyroidism with iodine in the hope of effecting a permanent cure. As has been pointed out previously, there is little or no clinical evidence to indicate that the course of the disease is altered by the administration of iodine. Too

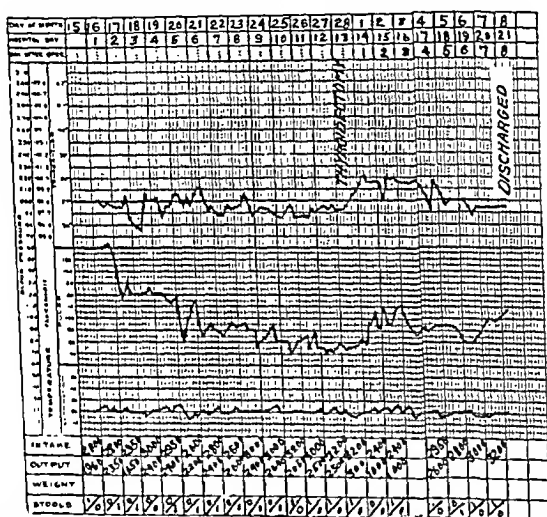


Fig. 63.—Note rapid fall of pulse curve in response to iodine and bed rest and the minimum reaction that followed thyroidectomy.

often, futile attempts to treat hyperthyroidism with iodine result in prolonged periods of disability followed by a final resort to surgery at a time when the severity of the disease is increased, the duration of the disease has consumed the patient's reserves of strength, and the risk of operation is greatly enhanced. If hyperthyroidism is recognized at the time of the appearance of its symptoms and if it is treated surgically without delay, the mortality rate is negligible and the period of disability is short.

The ideal time for performing a thyroidectomy is after

from one to two weeks of iodine therapy. One cc. of Lugol's solution or sodium or potassium iodide in equivalent doses provide an ample intake of iodine. This is given three times daily. Determinations of the blood iodine, taken one hour after the first dose of Lugol's solution, show values ranging from 125 to 175 γ per 100 cc. of blood as compared with the normal

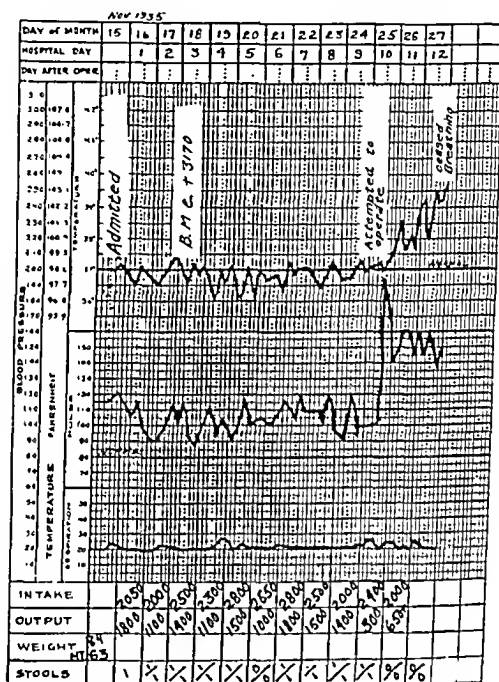


Fig. 64.—Note failure of pulse curve to respond to iodine and preoperative measures. At the time of operation, only nitrous oxide analgesia was given. The patient was draped but the pulse became so rapid that operation was postponed. Thyroid crisis developed and the patient died within forty-eight hours.

blood iodine level of 7 to 11 γ . No convincing or controlled evidence has been produced to indicate that the remission induced by the intravenous administration of iodides results in either a more rapid or a more complete remission of the hyperthyroidism, and in fact Thompson⁷ has shown that much smaller doses given by mouth are as effective as the larger doses that are commonly used.

When, in response to bed rest and iodine, the pulse curve has fallen and has established a plateau at a lower level, when the weight of the patient is increasing, when the patient's nervousness and restlessness are diminished, then the time for operation has arrived. The disease has entered a remission and has gained an impetus or "momentum" in the direction of recovery. After such a response, severe thyroid reactions are extremely rare and operation is safe.

If, on the other hand, the pulse curve fails to fall in response to bed rest and iodine, if the patient loses weight and becomes more nervous, then the disease has failed to enter a remission and is capable at the slightest provocation of evoking a dangerous thyroid crisis. This type of case, in which the pulse curve fails to respond to treatment, is commonly seen in those patients who have had iodine for long periods of time prior to admission, and the risk of operation here is greater than in the patient whose preoperative response has been favorable (Figs. 63, 64).

Iodine is effective in the preoperative treatment of both diffuse and nodular goiters. The toxic adenoma and the exophthalmic goiter both express themselves clinically as hyperthyroidism, and, although the most rapid and dramatic iodine remissions are apt to occur in patients with diffuse goiter, the remissions induced in patients with nodular goiter may be equally striking.

THE USE OF IODINE IN THE TREATMENT OF RECURRENT HYPERTHYROIDISM

It would appear to be inconsistent to denounce the use of iodine to cure primary hyperthyroidism and to recommend its use to cure recurrent hyperthyroidism. Nevertheless, clinical experience has shown that Haines⁸ is justified in his contention that the administration of small doses of iodine over a long period of time will result in lasting remissions in certain cases of recurrent hyperthyroidism. In our experience, the cases best suited for this therapy are those in which the recurrence is of short duration, of mild intensity, and associated with little or no palpable enlargement of the remnants of the thyroid gland. We have seen patients with this type of recurrence return a few years after thyroidectomy with symptoms of mild

hyperthyroidism and with an elevation of the basal metabolic rate up to plus 30 per cent. After treatment with 4 drops of Lugol's solution daily for a period of several months, the metabolic rate has fallen to normal, the pulse rate has dropped, and the symptoms have disappeared. The rationale of this procedure is difficult to explain on the basis of our knowledge of the action of iodine on primary hyperthyroidism. It is possible, however, that the interruption of the nerve and blood supply, accomplished by the previous thyroidectomy, may render the recurrent hyperthyroidism more susceptible to remissions and that the administration of iodine is sufficient to induce a permanent cure of the disease. It is also quite possible that the rare cases which respond to this type of therapy represent spontaneous remissions unrelated to the iodine therapy. In any event, experience has shown that the conservative management of *mild* cases of recurrent hyperthyroidism is justified and especially so in those cases associated with only slight enlargements of the thyroid.

THE POSTOPERATIVE USE OF IODINE

If a patient has been properly prepared for operation, iodine has been administered in sufficient quantities over a long enough period of time so that the remission of the hyperthyroidism is as great as can be obtained by means of rest and iodine therapy. In these cases, the level of iodine in the blood is extremely high and the thyroid gland has undergone as much involution as iodine can be expected to produce. Since the effect of iodine is on the secretory mechanism of the thyroid gland and since iodine does not have any effect on the active thyroid hormone which is already circulating in the blood, and finally since the thyroid in properly prepared cases has undergone as much involution as iodine can produce, it is quite useless to administer huge doses of iodine either by mouth, by rectum, or intravenously in an attempt to control a postoperative thyroid reaction in a patient who has been properly prepared for operation. The most that we can hope to accomplish after operation is to maintain the effects of the iodine given before the operation, and this can best be done by merely continuing to give 1 cc. of Lugol's solution three times daily, either by mouth or by rectum for the first three days after operation.

By this time, the peak of the thyroid reaction has passed and, except in the case of divided operations, the iodine can be discontinued with safety.

If, by any chance, a patient has been improperly prepared for operation and has not had sufficient iodine to produce a maximum remission, and if a severe postoperative reaction should develop, Lugol's solution in doses up to 50 minims can be given intravenously in a solution of 10 per cent glucose.⁹ This same treatment is effective for patients in thyroid crisis at admittance, especially if iodine has not been administered previously.

If iodine exerts an influence tending to produce a permanent remission in some cases of recurrent hyperthyroidism, it is logical to believe that iodine might tend to prevent such recurrences if given in selected cases after thyroidectomy. Therefore, it has been our practice to give small doses of iodine (3 minims daily) for a period of six months after operation in cases in which severe hyperthyroidism is associated with an *extremely hyperplastic gland*.

It is our clinical impression that the residual symptoms of hyperthyroidism are more promptly and completely controlled in these cases than would be the case if the patient were discharged without iodine and with the remnants of thyroid tissue in a hyperplastic state. This procedure seems even more logical in view of the known fact that iodine prevents the compensatory hyperplasia which develops in the thyroids of experimental animals after the greater portion of the gland has been removed.¹⁰

Occasionally, a simple endemic goiter is seen in which the early picture of iodine deficiency, *i. e.*, hyperplasia, is present. In spite of the marked hyperplasia of the thyroid, no hyperthyroidism was present in the case reported below. Had iodine in physiologic doses been administered from the time of operation. I feel confident that the recurrence could have been avoided.

The patient was a nineteen-year-old, unmarried school girl from Niagara Falls, N. Y., who entered with a history of having been born with a goiter. One brother had likewise been born with a goiter and was known to have hyperthyroidism. At the age of fifteen, the patient had had a thyroidectomy

because of progressive enlargement of the goiter. After operation, the goiter promptly recurred until it was nearly as large as before the operation.

Examination showed a recurrent, diffuse goiter of soft consistency. The basal metabolic rate was minus 7 per cent; the pulse rate was 78. There was no clinical evidence of hyperthyroidism.

Subtotal thyroidectomy was performed and the patient was discharged after an uneventful convalescence. At the time of discharge, the incision was well healed and no thyroid tissue was palpable.

One month later, the patient returned, complaining that her goiter had again begun to enlarge. Examination revealed a soft, diffuse enlargement of both lobes of the thyroid to approximately three times the normal size. There was no evidence of hyperthyroidism.

Checking back on the histology of the thyroid tissue previously removed, it was discovered that the gland had been in an extremely hyperplastic phase and that it contained no colloid whatsoever. In short, there was hyperplasia of iodine deficiency and the recurrence was caused by compensatory hypertrophy of the thyroid remnants. Had iodine been given from the first, the recurrence could doubtless have been prevented.

The second recurrence was treated with small doses of iodine and thyroid extract, and over a period of years decreased slightly in size.

THE USE OF IODINE BETWEEN THE STAGES OF A DIVIDED OPERATION

In the year 1926, iodine was widely used over long periods of time in an attempt to cure patients with hyperthyroidism. We did not then appreciate the danger of withdrawing iodine from patients with severe hyperthyroidism who had been taking iodine for a long period of time. It was thought that the effects of iodine lasted only a few weeks and that, after it had been administered for a time, it lost its effect. Therefore, in this year, iodine was not given between the stages of divided operations. If a pole ligation was performed for severe hyperthyroidism in a patient who had been taking iodine for a year, iodine would be withdrawn at the time of the patient's discharge from the hospital and the patient would be sent home to recuperate, with instructions to return in three months for the completion of the operation. In this year, as many patients died at home between the stages of divided operation as died in the hospital after operation. These patients left the hospital in good condition but, as nearly as could be judged from the correspondence with families and referring doctors, fatal thyroid crises or cardiac failure soon developed. In other words, the exacerbation resulting from the withdrawal of iodine

was more marked than the remission induced by the operative procedure and the net result was a fatal exacerbation of the hyperthyroidism. It is therefore unwise to discontinue the administration of iodine between the stages of a divided operation unless the patient can be kept under close personal supervision. The effect of withdrawal of iodine three days following a right lobectomy is shown in the accompanying chart (Fig. 65). The pulse rate fell in response to the lobectomy so long

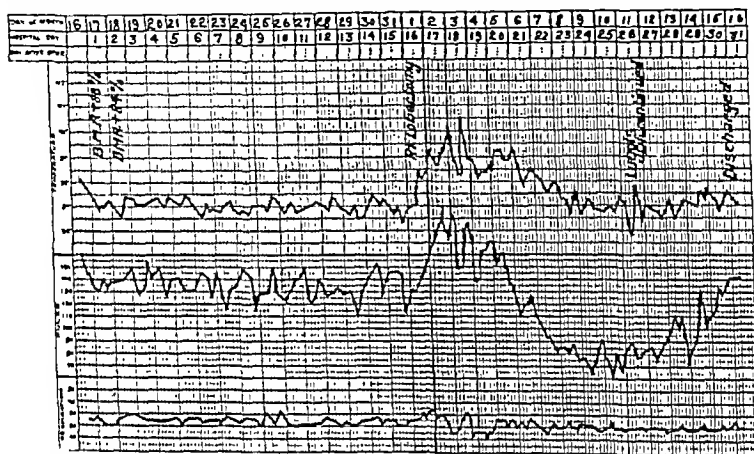


Fig. 65.—Note the rapid fall of pulse rate following right lobectomy. Iodine was discontinued on the third postoperative day and it is interesting to note that the pulse rate began to rise on the tenth postoperative day and by the fifteenth postoperative day had reached the same level as before operation. This shows the effect of withdrawal of iodine between the stages of a divided operation.

as iodine was given but, when the effect of the iodine on the remaining lobe wore off, the pulse rate promptly rose again nearly to its former level.

THERAPEUTIC TEST OF IODINE IN THE DIAGNOSIS OF HYPERTHYROIDISM

A course of iodine therapy is of definite diagnostic value in borderline cases of hyperthyroidism in which the basal metabolic rate is within normal limits. Occasionally, symptoms of hyperthyroidism will be unassociated with physical signs sufficiently definite to warrant a positive diagnosis. The basal

metabolic rate may be from zero to plus 15 per cent and, if the metabolism is carefully checked for four or five days until its level is definitely established, a significant drop to zero or below following the administration of iodine will establish the diagnosis of hyperthyroidism. If the patient experiences symptomatic relief as a result of iodine therapy, the diagnosis of hyperthyroidism will be further substantiated and thyroidectomy can be advised with assurance that the patient's symptoms will be relieved by operation.

SUMMARY

Iodine is of value in the treatment of hyperthyroidism under the following conditions:

1. In patients with diffuse or nodular goiters in preparation for operation.
2. In patients with mild recurrent hyperthyroidism associated with small goiters.
3. After operation until the peak of the thyroid reaction is over.
4. In small doses for a period of months after operation in patients with extremely hyperplastic glands.
5. Between the stages of a divided operation.
6. As a "therapeutic test" to aid in diagnosis.

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MEDICAL TREATMENT OF FLACCID PARALYSIS

WALTER J. ZEITER

PARALYSIS is defined as a loss of voluntary movement due to interruption of any part of the path of the motor impulses. The anatomical unit of the nervous system is known as the neuron. In its simplest form, at least two neurons are concerned in the transmission of a volitional motor impulse, these often being referred to as the upper and lower motor neurons or as central or peripheral neurons. Because a definite system of motor neurons convey motor impulses, it is not surprising that interruption of the nerve impulse in each is characterized by a distinctive symptom-complex. A lesion confined to the upper motor neuron usually is followed by what is known as the spastic type of paralysis, whereas, a lesion of the lower motor neuron alone produces the flaccid form of paralysis.

The degree of loss of power in muscles depends entirely upon the degree of injury of the nerve; when there is complete interruption of the nerve structure the result is complete paralysis.

The normal tone or tension of muscles is dependent upon the peripheral reflex arc which consists of the afferent fibers from the muscles which enter the cord by the dorsal spinal roots and terminate in synapses around the cells of the corresponding motor neurons in the ventral horn and of the peripheral motor neurons. When this arc is broken in any place, the muscles immediately lose their tone, as evidenced by softness and flabbiness to touch, and by lack of resistance to stretching which normally is present. Atrophy of the muscles is recognizable by a diminution in the size of the muscle, and by its soft and structureless consistency. A change is also noted in the electric excitability of the nerve and of the muscles it supplies.

Flaccid paralysis can be divided, for clinical purposes into two groups: (1) that due to a nontraumatic lesion of the nerve

and (2) that resulting from complete or partial section of a peripheral nerve. In the first group, the lesion may be situated in the anterior horn of the spinal cord, the anterior nerve rootlets, the peripheral nerve, or the muscle tissue. In the second group, the lesion occurs along the course of the peripheral nerve and is usually produced by an accident, trauma, or injury.

POLIOMYELITIS

A disease important in the first or nontraumatic group is poliomyelitis or infantile paralysis. This is an acute infectious disease which in the majority of cases is accompanied by a flaccid type of paralysis. The paralysis is not essential to the disease. It may be evidenced by weakening or total loss of motor power in certain muscles and groups of muscles with little or no gross disturbance of sensation. The muscles affected may be, and often are, in different parts of the body. The course of the disease may be divided into four stages as suggested by Legg:¹

In the first, or acute stage, the constitutional symptoms and preparalytic and paralytic phases occur. Treatment at this time should be entirely medical. Death from poliomyelitis in the acute stage of the disease is usually due to failure of the respiratory mechanism, this being caused by paralysis of the primary respiratory muscles, the intercostal muscles, and the diaphragm. In the last few years, definite advancement has been made in the treatment of this type of involvement by the use of the artificial respirator which has proved itself quite effective and efficient.

The second stage begins as soon as the temperature becomes normal and at this time the muscles may be definitely paralyzed or weakened. About 80 per cent of the patients will have sensitiveness, although others apparently never have any trouble with this symptom.

In this stage, the aim of treatment must be to prevent early deformities and relieve the tenderness. The latter can be combated by applying heat two or three times daily for fifteen to twenty minutes. The heat can be applied in the form of hot packs, hot wet blankets or towels insulated with rubber sheeting, electric pads, hot-water bottles, or radiant light

bakers. Legg believes that moist heat is more effective than the dry heat.

This stage may last from a few weeks to two or three months. Careful protection is necessary for the involved muscles in order to prevent stretching by the active muscles or by gravity. According to Carrell,² it is not necessary to make a detailed examination of the muscles at this time, because such a study would add injury to the muscles. A gross examination will supply the information needed to determine the group of muscles which require relaxation and rest. If, for example, several groups in the lower extremity are involved, it is well to place the legs in a neutral position with the feet at right angles to the legs and the knees straight. To maintain the correct positions, one can use wooden or pasteboard splints, bandages, plaster casts or plaster shells, covered bricks, cradles to support the weight of the bed clothes, pillows, sandbags, or rolled blankets. A lifting sheet is employed to assist in moving the patient.

The third, or convalescent stage, starts when the sensitiveness has disappeared and includes that period when the muscles make the greatest gain in power. It is at this point that active physical therapy can be started and a definite regimen instituted for reeducation of the muscles. Now a complete muscle examination is necessary to determine the extent of paralysis and their comparative strength before any intelligent physical therapy or reeducation of the affected groups can be undertaken. This must be done by someone who has a thorough knowledge of functional anatomy and the relative normal strength of the different muscles. This is true also in regard to treatment of these muscles. In handling these patients, it is desirable to have someone in charge who has had special training and experience in this special branch of physical therapy.

During this entire period, rest and support of the extremities is continued with adequate bracing and continued bed rest for a number of months. Fatigue and stretching of these muscles should be avoided because such activity makes it more difficult for the muscles to regain their strength and their chance of recovery will be definitely lessened. As the muscles gain in strength, the patient can be allowed more activity.

The therapeutic exercise pool will be beneficial to many patients. Its use seems particularly adapted to those whose muscles are so markedly affected that they are able to produce little or no motion when examined on a table. If these patients are examined in water, more motion will result than when examination is made outside the pool. This is not due to any special value of the water, but because of the release of gravity which permits the child to exercise the muscles better and allows greater freedom of different kinds of movements than would be possible on the table. Another advantage is that the warm water relaxes the muscles, improves the circulation, and creates more interest for the patient, thereby stimulating better cooperation. Where the large therapeutic pool is not available, the smaller but efficient Hubbard tank can be used for treating individual cases.

The fourth, or chronic stage, does not depend so much upon the number of months after the onset of the disease as upon the time when the condition seems to be practically stationary. The period at which no more improvement is noted after conservative muscle training usually occurs after eight to eighteen months have elapsed. It is usually possible to determine rather definitely at the end of a year what permanent inequality of muscle balance is going to persist. At this time, measures should be considered for stabilizing the joint. This may be done by operative procedures on the muscles or bones.

FOOD DEFICIENCY DISEASE OR AVITAMINOSIS

In such conditions, for example, beriberi which is recognized as a deficiency of vitamin B, the nervous tissues suffer injury. The peripheral nerves are affected first. They undergo degeneration and the muscles innervated by these nerves undergo atrophy. For these reasons, patients suffer from paralysis.

The important part of the treatment of this form of paralysis is to remove the cause. During the acute stage, supportive splints should be used to keep the extremity in a neutral position, thereby preventing contractures. Prolonged warm baths or some form of external heat, such as infra-red, may be used to relieve pain. After the acute phase has passed, gentle massage and muscle stimulation with the interrupted

galvanic current may be started. The current should be of just sufficient strength to cause a good contraction. The number of contractions will vary; usually it is well to begin with 3 or 4 and gradually increase the number. It is important in using these stimulations to avoid fatigue to the muscles.

MULTIPLE NEURITIS

Neuritis may be due to poisons introduced into the body from external sources, *i. e.*, metallic or inorganic substances as lead, arsenic, mercury, copper, alcohol, or various aniline compounds and derivatives. It may also be produced secondarily by toxins produced within the body from diseases such as typhoid, scarlet fever, smallpox, and diphtheria. Here again, the primary aim in treatment is to remove the cause. If paralysis occurs, it may be treated in the same manner as that following food deficiency diseases.

PARALYSIS DUE TO PERIPHERAL NERVE INJURY OR SECTION

Injuries to the peripheral nerves may be caused by falls, blows, dislocations, fractures, penetrating wounds, and continued pressure. If the injury is sufficiently severe, loss of power to the muscle is produced and flaccid paralysis results.

Pollock³ states: "Physical therapy holds the first place in the treatment of peripheral nerve lesions; operative procedure of suture and neurolysis will not serve to restore function. They only make it possible for the nerves to regenerate. It is conceivable that perfect regeneration might occur in the nerve and an extremity be functionless, because of interphalangeal fibrosis, retraction of capsular ligaments, marked atrophy and fibrosis of muscles, shortening of muscles, spasm of muscles, and ankylosed joints.

"Where a primary or secondary suture is indicated immediately, physiotherapeutic treatment must assist the operative procedure. When it is felt advisable to defer the operative procedure, physical therapy must be initiated promptly to the end that when the nerve regenerates it will activate a mechanism capable of adequate movement."

To protect the weakened muscles from contracting and overstretching, the same methods described for use in poliomyelitis can be applied. To supply heat to the affected parts,

the infra-red lamp or baker may be used. One must be careful, however, to avoid excessive heat because a disturbed sensation and lack of normal collateral circulation may cause unpleasant burns which heal slowly. The whirlpool bath at a temperature of 100° to 105° F. for twenty minutes to one-half hour is beneficial to the patient with cold, clammy and tender extremities. The medical diathermy also gives a very satisfactory form of heat. These treatments can be given for one-half hour; they should be of moderate intensity, for here too utmost care is necessary to prevent burns due to overheating.

After some form of heat is applied, electric stimulation is used. The slow sinusoidal current, beginning with 2 or 3 contractions of each muscle, is used at the beginning and is gradually increased. In patients with partial loss of function, more vigorous stimulation may be employed. The muscles should never be fatigued. Active exercise is instituted as soon as there is any indication of return of power. The interrupted galvanic current can also be used but it causes more pain and quite frequently is difficult to use in children and sensitive patients.

When active response of the muscles has returned, manipulation, active exercise, and reeducational movements form the important part of the treatment.

FACIAL PARALYSIS—BELL'S PALSY

The etiology of this condition must be taken into consideration before the treatment is initiated. Its causes are many and varied and the following should be borne in mind:

(a) This paralysis may be produced by the exposure of the face to cold or to a prolonged draft of air. This is commonly called "refrigeration" or the rheumatic type.

(b) Another common cause is disease of the middle ear and mastoid cells, both in the chronic and especially in the acute stages of the disease.

(c) Other causes are fractures of the skull through the petrous portion of the temporal bone; tumors and operations about the parotid gland and neck; basal meningitis, especially syphilitic; vascular, neoplastic, and inflammatory conditions within the pons.

The first important step in treatment is to remove the causa-

tive factor if this is possible. Neoplasms, of course, constitute a problem in surgery. If the paralysis is due to syphilis, active intensive therapy should be started. During the early stage of paralysis, rest of the involved muscles is essential and no attempt should be made to exercise the muscles at this time. It is well to give some support to the muscles to prevent marked sagging, and this can readily be done by running narrow strips of adhesive tape from the region of the temple down the cheek to near the lips.

During this early stage, some form of heat should be applied to increase the circulation to the involved part, to reduce inflammation, and to speed up absorption of exudate. Hot compresses, with or without magnesium sulfate, infra-red radiation, and medical diathermy give a desirable form of heat. The hot compresses serve as a simple method which is easily and readily adaptable for home use. Infra-red radiation is simple to apply and gives a penetrating form of heat. The use of the short-wave diathermy by the electromagnetic induction method is the simplest method of securing a soothing deep heat.

During this period, it is well to treat the patient two or three times daily. If there is much pain, positive galvanism for its sedative effect should be employed over the painful area. After a week or ten days, when most of the pain has disappeared, very gentle massage to the cheek may be used but this should be preceded by some form of heat.

Following the acute symptoms, which usually last from ten to fourteen days, the disease enters the stage of degeneration of the nerve. At this time, a thorough examination of the nerve and muscles should be made by electrodiagnosis which will help in making a prognosis and will also give some information regarding the intensity of treatment. More intensive treatment should now be started. Voluntary exercises should be tried daily. The patient should stand in front of a mirror and try to smile, close the eye, lift the eyebrow and reproduce all facial movements of which a normal person is capable. Heat is applied to the affected side for fifteen minutes followed by the interrupted galvanic current and massage is given. This form of treatment may be continued for several months or for a year if necessary.

BRACHIAL PLEXUS PARALYSIS

Brachial plexus paralysis is usually one of two types: (1) Erb-Duchenne¹ palsy or the upper arm type, (2) Klumpke palsy or the lower arm type. Paralysis of the entire arm may occur and this is a combination of the Erb and Klumpke types.

These various forms of paralysis of the brachial plexus may be produced by fractures of the cervical vertebrae, by diseases involving the cervical vertebrae such as tuberculosis, syphilis, tumors in the cervical region, cervical ribs, dislocation, fracture of the shoulder girdle or humerus, by penetrating wounds and by stretching of the brachial plexus at birth.

The treatment is started as soon as the palsy occurs. During the acute stage, while tenderness and pain are present, rest is of utmost importance. To obtain rest, corrective splinting must be employed to avoid any pull or tension on the plexus. This can be obtained by use of the aeroplane splint or in birth injuries by use of the obstetric splint. While waiting for nerve regeneration to occur, heat, massage, passive exercise, and electric stimulation should be used to prevent atrophy of the muscles. Heat can be applied with an infrared generator, hot-pad, diathermy, or the whirlpool bath. Massage should be used to help stimulate the circulation and absorb any fluid that may be present in the extremity. Passive motion should be done slowly and gently. This helps to prevent contractures and keeps the joints mobile. In carrying out any of the above procedures, it is always important to avoid any pull or stretching of the brachial plexus.

No attempt is made to include types of flaccid paralysis which may be caused by disseminated changes in the central nervous system and so-called "primary diseases" of the muscle.

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DIAGNOSIS AND TREATMENT OF HYPO-OVARIANISM

E. PERRY McCULLAGH

OVARIAN deficiency is a common clinical condition. The cases in which ovarian failure is seen can be considered broadly to fall into 3 groups according to the degree of severity of the involvement, although the fundamental factors are closely related in almost all cases.

The first group is comprised of women in whom there is outspoken evidence of an endocrine abnormality. In the presence of a few of these, such as myxedema or the climacteric, treatment may be expected to yield uniformly good results but, in the remainder of the group, if the condition is sufficiently severe to produce outstanding signs, it may have been present for a long time and will yield poorly to therapy, especially with respect to the menstrual periods.

In the second group are those cases which simulate definite endocrine syndromes, the features of which indicate the mechanism through which ovarian function is involved.

In the third and largest group, there may be little or no clinical evidence of the cause of abnormal ovarian function except abnormality in menstrual periods.

In the latter group, although the condition is not so severe as in the others, it may be more vague and, to the same degree, treatment becomes more empirical. It has been necessary to assume that in mild abnormalities of menstruation, the factors involved are fundamentally the same as we understand them to be in severe endocrine disease. Even though this is the case, the therapist is still at a disadvantage because of the relative inadequacy of the available active principles. This applies particularly to pituitary principles. In addition, there is a lack of knowledge relative to their proper use, and finally their cost is high.

It has been deplored by many writers that it may be necessary to continue treatment to prevent recurrence of symptoms

such as amenorrhea for example. Such continuation of treatment is not surprising if we consider that this is true with any replacement therapy. No clinician is dismayed if, after discontinuing the use of insulin or thyroid, it becomes necessary to give it again. When we consider the many obstacles involved, it seems, in fact, rather remarkable that so many instances remain in which a relatively permanent result is obtained following the use of sex hormone therapy which has been given over a relatively short period of time.

A cursory review of some of the more definite endocrine disorders will serve to give a broad view of the very intricate problem of hypo-ovarianism as seen clinically, and will also afford an opportunity for mentioning certain features of ovarian failure which may apply to milder and less definite clinical conditions where menstrual abnormalities are likely to be the chief complaint.

Hypothyroidism is a common cause of menstrual disorders, since it is in itself a very common endocrine disease, especially in combination with other endocrine abnormalities. Fully developed myxedema is uncommon and, in cases of hypothyroidism without obvious myxedema, the possible presence of the condition must be borne in mind and symptoms and signs must be elicited and evaluated with care if the correct diagnosis is to be established. There is still a tendency to make a diagnosis of hypothyroidism based on a low basal metabolic rate alone. Such a practice undoubtedly leads to erroneous diagnoses, yet at the same time there are few hypometabolic states in which the cautious use of thyroid does actual harm; in fact, in a great many instances where menstrual abnormalities are the chief reason for treatment, small doses of thyroid are of value regardless of whether a diagnosis of hypothyroidism can definitely be established. Haines and Mussey¹ have shown, for example, that in 75 women with various menstrual disorders and low basal metabolic rates without myxedema, there was an improvement in menstrual function in from 55 to 72 per cent following thyroid feeding alone. The doses employed varied from 0.5 to 3 grains of desiccated thyroid daily.

In 194 of our patients with a clinical diagnosis of hypothyroidism before determinations of the metabolic rates were made, 53 per cent were found to have metabolic rates below

minus 20 per cent, and 47 per cent between minus 20 per cent and ± 0 per cent. The percentage of frequent signs and symptoms was as follows:

<i>Symptoms</i>	<i>Per cent</i>
Diminished endurance	93
Diminished energy	89
Mild nervousness	79
Drowsiness	78
Inalertness	74
Dry skin	74
Poor memory	68
Numbness of hands or feet	67
Edema	67

Edema was considered to be present if any puffiness of the hands or eyelids was noted by the patient.

In this group of 194 patients, there were 164 women, of whom 36 had passed the menopause. Of the remaining 128, 90 had normal menstrual function. The menses were judged to be abnormal in 38 (29.7 per cent), all mild grades of abnormalities being included. Among these abnormalities, irregular bleeding occurred in 54 per cent, menorrhagia in 39 per cent, and hypomenorrhea in 54 per cent, these symptoms overlapping in some cases.

Adrenal cortical adenomata or hyperplasia may be accompanied by obesity, masculinization, male distribution of hair, coarse voice, and enlargement of the clitoris. All the other features ascribed to pituitary basophilism have been reported to be present in some cases of adrenal tumor. It is extremely difficult to differentiate this condition from pituitary basophilism or from arrhenoblastoma of the ovary and at times it is impossible. It has been suggested that arrhenoblastomata cause less enlargement of the breasts and tend to produce more clean-cut masculinization in other ways such as obvious laryngeal hypertrophy and enlargement of the clitoris. It is difficult to state whether the association of amenorrhea with such conditions is due to a true hypo-ovarianism. If distinct hypertrophy of the adrenal or the presence of a tumor is proved by injection of air or exploratory laparotomy, operative removal of part of the adrenal may be followed by resumption of normal menses. In mild cases, treatment similar to that used for

hypo-ovarianism of primary or pituitary origin may be tried or roentgen irradiation may be administered to the pituitary or adrenal.

Ovarian hypofunction occurs in many outspoken diseases of the pituitary and, in mild cases, the matter is probably on a similar basis.

Pituitary cachexia (Simmonds' disease) is complete or almost complete suppression of pituitary activity due to organic destruction of the gland. The symptoms are those which may be anticipated where there is a marked reduction of all endocrine functions. In females amenorrhea invariably occurs. Extreme weight loss and weakness is found. Arterial hypotension is present. Marked depression of the basal metabolic rate to minus 35 or minus 40 per cent without myxedema is common, and hypoglycemia occurs. All other causes of severe cachexia must be carefully excluded and among the most difficult is Addison's disease. Chronic infections, such as tuberculosis, cause a similar picture but are less likely to produce such a great depression in metabolic rate or such early amenorrhea. The treatment consists of the use of a high calorie intake. This is always difficult to attain because of anorexia. The use of large doses of vitamins is indicated. Thyroid, if used at all, must be given with the greatest caution, bearing in mind that similar depressions of the basal metabolic rate are caused by starvation alone. Adrenal cortical hormone and high sodium, low potassium intake may be tried as well as polyvalent pituitary extracts, for example, polyansin (Ayerst).

A condition which simulates pituitary cachexia very closely is **anorexia nervosa**. This should be considered as a clinical syndrome since it is apparently possible that an individual may voluntarily restrict the diet to such a degree as to produce all the essential features of the disease just mentioned, except perhaps the organic destruction of the pituitary. This condition is important in the discussion of ovarian failure because these similar states probably form a counterpart in very severe degree of food or vitamin deficiency which, in mild form, cause ovarian failure more frequently than is demonstrated by our present means of examination. It is not uncommon for amenorrhea to follow the injudicious restriction of diet, and

food deficiency should always be considered as a possible factor in the production of menstrual abnormalities, especially in those cases where no endocrine disorder is apparent.

Pituitary basophilism in its typical form includes such symptoms and signs as early amenorrhea, obesity, chiefly of the trunk, neck and face, hirsutism, purplish striae, arterial hypertension, and decalcification of the skeleton. Hypertrophy of the clitoris may be present. Common additional findings are elevated metabolic rate, decreased glucose tolerance, polycythemia, and sometimes high levels of serum calcium, blood cholesterol, and nonprotein nitrogen. The essential mechanism involved here is apparently excessive activity of the basophilic elements of the pituitary which, in turn, cause an increased stimulation of the adrenal cortex. Basophilic adenomata have been reported in many such cases although it should not be overlooked that they have also been reported in many other cases in which there was no such clinical syndrome. The combination of basophilic adenoma and adrenal hypertrophy or adenoma is apparently much more commonly associated with this syndrome. The disease must be differentiated from adrenal cortical syndromes and arrhenoblastomata of the ovary. The complete differentiation may be clinically impossible with any degree of certainty. Estrogenic substances in the urine are frequently low, but in some cases they are well within normal range in the presence of menstrual irregularities or amenorrhea.

The treatment of choice is roentgen irradiation of the pituitary or of the pituitary and adrenals.

Cases which simulate a less marked syndrome of this sort are common and although I know of no method of proving the relationship, it is highly suggestive. Frequently young women are seen who are obese, have moderate hirsutism, amenorrhea, or oligomenorrhea, but no other clinical findings of note. The blood pressure may be mildly elevated. Assays of estrogenic hormone may, when available, help in formulating a rational plan of therapy. If a properly balanced, low calorie diet, plus the type of therapy outlined below for other types of hypovarianism fail, irradiation of the pituitary gland should be considered and will be successful in some cases.

Other pituitary diseases might be mentioned such as in-

fantilism in which there is dwarfism which may not be associated with the retardation of epiphyseal development unless there is concomitant hypothyroidism. The epiphyseal lines may long remain open, however, due apparently to the severe hypogonadism which is usually present and brings with it the marked underdevelopment of genitalia and secondary sexual characteristics. The numerous other causes of dwarfism must be excluded. Treatment by growth hormone has been, on the whole, very disappointing. The administration of thyroid to the limit of tolerance is usually indicated, and every effort should be made to maintain the best possible nutrition. The treatment of the hypo-ovarianism itself is usually postponed through the fear that more normal levels of ovarian hormone in the body may hasten epiphyseal closure. In this, we probably compliment ourselves, exaggerating in our own minds the ease with which genital development and retarded epiphyseal union may be corrected. It is perhaps better, however, to err on the safe side and, when growth has finally become stationary, intensive sex hormone therapy, if prolonged for six to twelve months or more, will produce growth of the genitalia and secondary sexual characteristics sufficient to validate the effort and expense involved. A menstrual period in severe cases may be attained but a normal sexual rhythm cannot be expected.

Gigantism is uncommon in women. When it does occur, it is likely to be associated with hypo-ovarianism. The treatment of choice for the gigantism is roentgen irradiation of the pituitary and, if it is warranted, the hypo-ovarianism must be treated on its own merits. Here again, assays of estrogenic hormone may be of value.

In women, acromegaly occurs much more commonly than gigantism. Patients with moderately advanced acromegaly may menstruate normally and advance through pregnancy. In some instances, in fact, symptoms apparently are ameliorated during pregnancy. Hypomenorrhea or amenorrhea, however, is the rule.

The general symptoms are associated with enlargement of the skeleton, especially the head and extremities, as well as the soft tissues. A tendency to goiter, hyperthyroidism, arterial hypertension, and diabetes is common. Acidophilic pituitary

tumors may cause headache, erode the sella, or extend upward where they produce signs of pressure and blindness. The choice of treatment lies between roentgen irradiation and surgery and depends upon the rapidity of increase in the size of the tumor which is usually present, the symptoms of pressure, and especially the degree of loss of vision. Large doses of estrone (follicular hormone) may be tried in mild cases. Roentgen therapy seldom corrects the hypo-ovarianism to a practical degree or reestablishes the menses. In some of these cases, the urinary prolactin is excessively high and, in some cases of amenorrhea, there is a normal excretion of estrogens. Whether these are normal in the blood, I cannot say. If these substances are low, treatment for the hypo-ovarianism, if indicated at all, will be as for other instances of pituitary hypo-ovarianism.

Adiposogenital dystrophy (Fröhlich's syndrome) was originally thought to be due to hypopituitarism but it is now generally accepted that it is due to hypothalamic damage alone or with pituitary damage. Originally, the syndrome included a tumor in the immediate vicinity of the pituitary but, currently, Fröhlich's syndrome does not usually imply the necessary presence of a tumor.

Especially in children, an acute infection frequently precedes the onset of obesity but acute infections are so common as to render judgment regarding their relationship difficult.

Occasionally, however, more definite evidence of mild encephalitis can be obtained. The appetite and thirst are usually excessive and it is probable that these, associated as they often are with diminished physical activity and a basal metabolic rate somewhat lower than normal, form the basis for the obesity.

In girls, puberty is delayed, although it seldom fails to appear. At the age of seventeen to nineteen, these obese girls may have little or no pubic or axillary hair, they commonly have small, conical breasts, smooth pink areolae and infantile nipples. The vagina is small and the uterus, if it can be felt, is smaller than normal. Normal sexual interest is obviously lacking. The teeth are excellent, the epiphyseal development and union are about normal except where there is concomitant hypothyroidism. The skin is fine, soft, and hairless. The

obesity is confined chiefly to the trunk and attachments of the extremities. Mild cases grade gradually into normal. The treatment of the hypo-ovarianism is part of the treatment of the entire condition. In the more severe cases, injections of one of the preparations of pregnancy prolan is indicated (antuitrin S, Parke, Davis and Co.; follutein, Squibb; A.P.L., Ayerst; antophysin, Winthrop, and many others are available). Apparently, adequacy of dosage and prolongation of treatment are the essential considerations. It has been our practice to give 200 or 300 units three times per week, prolonging the treatment for a year or more if necessary. Usually two or three months is an adequate length of time. The treatment may be given continuously or for three weeks of each month, the latter being theoretically preferable. A.P.L. may be obtained in a strength of 500 units per cubic centimeter though these Collip units are smaller than those used in other solutions.

Reduction of weight is important. In adolescents, a diet containing 20 to 30 per cent more than the basal caloric requirement for ideal weight will usually produce excellent results and will not mean enough restriction to cause the patient to abandon it. In adults, a diet of between 800 and 1200 calories is usually practicable. In either case, the diet should contain at least 0.85 Gm. of protein per kilogram of ideal body weight in addition to adequate vitamins and minerals. It is frequently advisable to add extra amounts of vitamin B in the form of yeast tablets or combined with vitamins A and D as one of the available vitamin-concentrate capsules such as hepicoles compound (Lilly) or abdol (Abbott). The administration of thyroid in small doses is often a useful adjunct, but the administration of the usual doses of pituitary extract by mouth is useless.

PITUITARY HYPO-OVARIANISM

In such outstanding pituitary diseases as acromegaly, dwarfism, or true pituitary cachexia, the pituitary origin of hypo-ovarianism is unquestionable. In addition, however, there are certain cases of pituitary tumor in which evidences of ovarian deficiency are the only signs of endocrine disease and on this basis it seems reasonable to assume that functional ovarian disorders may begin with pituitary damage. Parkes²

and Evans and Simpson³ showed that in rats vitamin B deficiency may cause ovarian damage in this way.

Clinically, the differentiation between primary hypogonadism and that of pituitary origin may not be possible with any degree of certainty. If peripheral signs other than hypogonadism are present and point to the pituitary, this gland is suggested as the seat of the abnormality. This is true also if examination of the visual fields or roentgen examination shows evidence of local disease.

In the young who fail to menstruate after the age of sixteen or in whom the menses remain irregular or very scant, hypofunction of the pituitary may be suspected. In later life, such patients are likely to be sterile. If other diseases, such as hypothyroidism, congenital deformities, anemias, and chronic infections, are carefully excluded, such a possibility is even more probable. Examination in these patients reveals poor development of the vagina, small size of the uterus, scant production of pubic and axillary hair, and small breasts.

In adults, where the condition has supervened after a period of normal or relatively normal sexual development, there is little to distinguish the case from one of primary ovarian failure. In most adults with severe, primary, ovarian damage, there is little change in the skin or hair while, in some of those with pituitary failure, there is a peculiar and at times almost complete disappearance of axillary and pubic hair which is coupled frequently with a very fine, pale skin and marked loss of sexual impulses. In such cases, prolan assays are of some value. No method of prolan assay has been developed by which one can determine that there is a pituitary deficiency but most of the methods such as the Aschheim-Zondek or Friedman test will measure excesses of pituitary or pituitary-like hormone in the urine. If this material is excessive in the presence of hypogonadism, it strongly indicates, in most cases, that the pituitary disease is not the origin of the hypogonadism. Even this evidence, however, must be accepted with caution since some patients with pituitary tumor and amenorrhea can be shown to have positive Friedman tests.

The importance of making a differentiation between pituitary hypogonadism and primary ovarian failure is supposed to be of importance in treatment. It is argued that, if pit-

uitary failure is present, the use of ovarian hormones will aggravate it, whereas, if pituitary sex hormones are present in overabundance because of ovarian failure, such products as pituitary sex hormone or pregnancy prolan are contraindicated. There are fallacies in both arguments. Where ovarian failure is secondary to pituitary disease, raising the level of ovarian hormones to near the normal range by injecting them should have no greater inhibiting effect upon the pituitary than would normal ovarian activity. It is known that very large doses are required to bring the estrogens in the urine up to or above the normal range. In the case of excessive urinary prolan, the prolan measured in the urine in pituitary disease probably is not the same substance as the pregnancy prolan usually used for treatment. In cases of menorrhagia at the menopause, excessive amounts of urinary prolan may be present. This has been shown by Engle⁴ and others to be chiefly follicle-stimulating hormone. Even in cases where there is excess of such hormone, the injection of extracts of pregnancy urine may relieve clinical symptoms.

MENORRHAGIA

According to current theories, functional menorrhagia in young women is due to a limited pituitary action which produces an active follicle but does not force such a follicle to rupture and form a normal corpus luteum. The continued action of estrone from such a follicle thus causes excessive endometrial growth with persistent characteristics of that type of endometrium normal to the preovulation period. Such endometrium may become thickened, cystic, and finally degenerated and hemorrhagic.

There are many arguments against this conception. First, in doing endometrial biopsies in cases of menorrhagia in which organic causes such as tumors and inflammation have been excluded, one may find a definitely hypoplastic endometrium. Second, it has been demonstrated repeatedly that persistent follicles may be present in the ovary without menorrhagia, and third, corpora lutea which appear normal on histologic examination may be present even though functional menorrhagia exists. In addition, no evidence has as yet been produced to show that injections of pregnancy prolan actually cause lutein-

ization in the human ovary. In spite of these apparent objections, functional menorrhagia, both in the young and at the menopause, if the patients are carefully selected, responds remarkably well to injections of extracts of pregnancy urine.

In severe cases of pituitary hypo-ovarianism, we use the following plan of treatment which is modified to suit the individual problem:

The diet is given consideration, a well-balanced diet being arranged with more than sufficient vitamin B. Reduction of weight is produced when the weight is excessive. Thyroid in doses of $\frac{1}{2}$ to 1 grain of the desiccated gland is frequently used as an adjunct to treatment. Pregnancy prolan (antuitrin S, follutein, etc.) in doses of 100 to 300 units is given three times per week. In cases of amenorrhea, this may be continued for three weeks at a time and then be interrupted. During the first half of the treatment, pituitary sex hormone such as prephysin (Chappel) may be used alone or in conjunction with the agents mentioned above. In addition, where severe hypogonadism is present, estrone in the form of progynon B, theelin, amniotin, etc., is given in doses varying usually from 5000 to 10,000 units for 6 to 9 doses, each dose being given with one of the doses of pregnancy prolan.

In menorrhagia in women under thirty years of age, no curettement is done as a rule. When the patient is over this age, care must be taken in excluding malignancy. In cases in which menorrhagia has lasted for many months, a curettement preceding endocrine therapy is frequently advisable, both to determine the type of endometrium present and to remove the abnormal endometrium. In cases of severe bleeding, transfusion may rarely be necessary. Pituitrin or ergot may be used if necessary at first. Sometimes a few injections of mocassin venom will be effective. The possible factor of mild hypothyroidism should be remembered and, where any suspicious evidence is present, it is good practice to give $\frac{1}{2}$ to 1 grain of desiccated thyroid per day. Ferrous sulfate in doses of 3 to 10 grains three times a day will usually help materially in repairing the anemia which so frequently is present.

Since 1931, when Novak⁵ proposed the use of pregnancy prolan in menorrhagia, it has been widely employed. Success of treatment has varied greatly in different hands. The

variability is probably associated with the thoroughness with which treatment is given and the care used in selection of cases. Many plans have been proposed for such therapy. I have been convinced for several years that our success has been more consistent in those patients who received large doses of the substance. In spite of the cyclic nature of the menses, we have used regular injections, disregarding the time of the period. As a rule, doses of 100 to 400 units of antuitrin S, follutein, or 500 or more units of A.P.L. are given. Good results have been obtained in about 90 per cent of our cases. In most of the failures, the doses were small and were given for a short time only. In a few instances, pelvic inflammation which was unrecognized at first was suspected as a cause of failure. In some cases, however, there was typical hyperplastic endometrium, adequate dosage, complete failure of treatment, and no tenable explanation. In one instance, after all the above methods failed, use of moderate doses of cevitic acid was followed by normal menses. Apparently deficiency of vitamin C should be considered as a possible cause of uterine as well as other forms of hemorrhage.

Treatment with pregnancy urine extracts usually need not be continued longer than three months unless definite evidence of improvement is obvious. Usually one or two months of treatment is sufficient. In a small proportion of cases, the symptoms will recur and usually will respond again to treatment.

PRIMARY HYPO-OVARIANISM

Severe, primary, prepuberal hypo-ovarianism is quite uncommon. The diagnosis seems to be warranted where there are outspoken evidences of ovarian failure which antedate puberty without any evidence of other glandular disease. It is difficult to see the logic of classifying such cases as pituitary in origin when it is not certain that such is the case, even though it may be conceded that such is possible. In these cases, the vagina and uterus remain infantile and the menses fail to appear, the breasts do not develop, axillary and pubic hair are sparse or absent, and the labia are small. The epiphyses remain open for a long time, and the arms and legs become long, the span at times exceeding the height by 4 or more inches. The trunk and extremities are usually thin, are

covered with fine skin, and are almost hairless. The facies are puerile. There is a tendency to fatigue, and a bearing typical of adult assurance and sexual interest is lacking. A general childlike demeanor is preserved. There is little laboratory data of note in such instances. Estrogens in the urine, if present at all, are in very small amounts; urinary prolan may be demonstrated.

The treatment in such cases, so far as has been demonstrated, can be expected to bring about only limited effects. Relatively large doses of estrone alone, such as 2000 to 10,000 units of theelin, progynon B or similar substances about three times per week, if continued for months, will cause distinct growth of the genitalia and breasts and appearance of axillary and pubic hair. Pregnancy prolan, in doses of 200 or 300 units at the same intervals, continued over long periods might be expected to yield similar results.

In milder cases where a moderate development of the genitalia is present or can be produced by treatment, it may at times be advantageous to bring about an artificial menstrual period. This may be done by giving 60,000 to 100,000 units of estrogenic hormone, usually in doses of 10,000 units every second day, planning the treatment in such a way that the last injection is given four days prior to the calculated menstrual time. On the last four days of such a course of treatment, progestin may be given daily in doses of $\frac{1}{2}$ to 5 units per day as lipolutein (Parke, Davis and Co.) or proluton (Schering). If not successful at first, repetition of such measures will usually bring about what is apparently a normal menstrual flow. This is sometimes accompanied by numerous, vague, disagreeable symptoms. In a few cases, milder treatment later has been followed by regular menstrual periods. In mild cases, where there seems to be reasonable hope that normal menses may be brought about and if the general clinical picture warrants it, pregnancy prolan in moderate doses may be used with each injection of estrogenic hormone. Such treatment is bothersome to the patient as well as expensive, and probably should not be attempted unless the patient is cognizant of the probable nature of the result. In some cases, the appearance of a single menstrual period may have sufficient psychic value to be warranted.

Severe adult hypogonadism is seen in the adult castrate. It produces signs and symptoms in all essential respects identical with those which may be seen at the menopause. Here the symptoms are much more marked than in early hypogonadism, but the physical signs are less striking. After castration, there is some atrophy of the uterus, the vaginal mucosa loses its rugae, the breasts become flabby. There is little if any change in body hair. The basal metabolic rate may be decreased mildly and body weight increased, especially over the abdomen, the trochanters, and about the lateral malleoli. In cases of long standing, the genital atrophy may be associated with vaginitis or kraurosis which may be greatly helped by estrogenic hormone therapy. The outstanding symptoms are chiefly of nervous and vasomotor origin. Among the common symptoms are nervousness, excitability, irritability, emotionalism, a tendency to melancholy, headache, and insomnia. Hot flushes or chills are almost constant, at least for a time, and they may persist for as many as twenty-five years or more. Hyperhidrosis often accompanies such flushes. Tachycardia, palpitation, and dyspnea are common. Hypertrophic arthritis may be greatly aggravated in some cases by ovarian failure which presumably takes place by the addition of a further metabolic burden to the tissues. In such cases, ovarian replacement therapy may help materially in controlling symptoms due to such arthritis.

Whether involutional melancholia can be ascribed entirely to ovarian failure, as is believed by Werner,⁶ is doubtful in the minds of most workers. It seems quite apparent, however, that the condition may be precipitated or aggravated by ovarian failure in many instances and, in like manner, may be relieved in large degree by adequate estrogenic hormone therapy. In such cases, we have given doses sufficient to control all menopausal symptoms which were present and continued with smaller doses for weeks or months if the symptoms of melancholia persist.

Symptoms similar to those seen at the menopause may occur months or years prior to the cessation of the menses and may be due to partial removal of the ovaries, irradiation, or inflammation such as gonorrheal oophoritis or to severe generalized infections such as undulant fever. In such cases.

nervous symptoms frequently make their appearance from a few days to two weeks prior to the menstrual period and often include simple irritability, a tendency to melancholy, sore, swollen breasts, and headache. The headache may be generalized, often at the vertex and sometimes distinct migraine is precipitated.

These symptoms are almost invariably amenable to injections of estrogenic hormone alone or accompanied by 100 to 200 units of pregnancy prolan every second day during the second week of the cycle. With respect to the headaches, clinical judgment will usually dictate approximately the likelihood of other factors of importance being present which are as a rule better investigated and treated along with the hypovarianism.

Dysmenorrhea in a few cases is associated with signs of mild hypo-ovarianism such as small uterus and somewhat sparse secondary sexual characteristics. In these, permanent relief may result following the use of 2000 to 5000 units of estrogenic hormone every two or three days for two or more months. In others in whom there is no evidence of endocrine or other disease as a cause of the menstrual pain, pregnancy prolan in doses of 100 to 300 units three times a week, given preferably for two weeks prior to and during the menses, may be effective. In some of these, the addition of $\frac{1}{10}$ to 1 unit of progestin as proluton (Schering) or lipolutein (Parke, Davis and Co.) may give temporary relief. In cases such as the above, pregnancy forms the physiologic cure. Dilatation and curettage is effective in a very small proportion. In severe cases, endometriosis must be considered. The effect of regular exercise is often excellent and all factors causing excessive pelvic congestion such as constipation or sexual excitement should be avoided, especially near the menstrual time. For the pain itself, atropine or ephedrine will sometimes be effective; otherwise heat, mild analgesia, or small amounts of alcohol, if acceptable, will usually give material symptomatic control.

Mild symptoms of the menopause may be relieved at times by remarkably small doses of ovarian hormone. One or 200 to 1000 international units as theelol (Parke, Davis and Co.), menformon or progynon D-H (Schering) daily are frequently

effective. In more severe cases, we prefer to begin by obtaining complete control of symptoms as rapidly as possible. Injection of larger doses is valuable for this purpose and the severest symptoms of the menopause may almost invariably be completely controlled if the doses are sufficient. Progynon B, theelin, and amniotin are a few of the many preparations of estrogens in oil which are available in doses of 2000 to 10,000 units or more per cubic centimeter. If a watery solution is desired so that the patient herself may inject it with as much ease as insulin, aqueous menformon (H. H. Beisner) serves well. Usually 2000 units every day for a few days is given and then every second day will suffice. In many, 5000 units every second day gives more complete relief and in a few, doses of 10,000 units every second day or even daily for a time may be necessary. When symptoms are relieved, the dose may be reduced or oral medication used.

Endometrial biopsies may be of considerable value in the diagnosis of hypo-ovarianism. It is not possible here to dwell in any detail upon such a subject. It has been our practice to use a Novak⁷ suction curette, obtaining several scrapings. This seems important since some endometrium shows areas varying widely in nature. Wherever it is possible, such a curettement is done two days before an expected period. In multiparae, it may be done in the office and in nulliparae it is usually performed under nitrous oxide. Such a procedure is valuable in doubtful cases and endometrium from the later part of the cycle is especially desirable since, normally, it shows the full effect of follicular hormone plus that of luteal hormone.

In those cases in which assay for estrogenic hormone is desired, we prefer to collect twenty-four-hour specimens of urine once or twice about the middle week of the menstrual cycle. The procedure which we have found most useful utilizes the method of extraction described by Koch.⁸

The twenty-four-hour specimen of urine is hydrolyzed with hydrochloric acid, extracted in a special extractor with benzol for two hours, and the extract is taken up in 30 cc. of oil. Six adult spayed female rats are injected with 10.5 cc. of the extract. Two rats receive 0.75 cc. each, two 1.5 cc. each, and two 3 cc. each. Vaginal smears are taken forty-eight, sixty,

and seventy-two hours following the injections and it is established by estrus smears whether the number of rat units of hormone in the total extract lies below 10, from 10 to 20, 20 to 30, 30 to 40, or 40 or over. This method is to be published from our laboratories. If desirable from a clinical standpoint to arrive at a more exact determination, a second series of injections is done, utilizing 10 spayed rats, and adjusting the dose in such a way as to determine this point. The normal level is considered to be 30 or more rat units by this procedure.

In conclusion, the treatment of functional menorrhagia and treatment for the control of symptoms of primary hypo-ovarianism in the adult may be said to be highly satisfactory. In the remainder of the hypo-ovarian states, less regular results are obtainable. If the maximum effectiveness is to be obtained from treatment, the patient must be thoroughly considered from all angles, especially with respect to the endocrine system. Endometrial biopsies and hormone assays may be used to considerable advantage and treatment for the most part should be intensive and persistent.

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THE TREATMENT OF SCIATICA

JAMES I. KENDRICK

IN the treatment of sciatica, it is necessary to realize that the sciatica or sciatic pain is invariably not in itself a clinical entity but rather a symptom. This realization has constituted the greatest advance in attacking this often very chronic and disabling condition. Better understanding of the underlying etiologic factors has developed following the use of better methods for investigating the patient. Certainly, the clinical picture and the general examination often are not sufficient to determine the exact etiology and, without modern methods for examination, we might be satisfied to call sciatic pain sciatica and treat the patient's symptoms.

The treatment of sciatic pain will be much less of a problem to the clinician if he will decide that the condition is not incurable and that an analysis of the information presented in the history, the examination, the laboratory work, and roentgen examination will usually reveal the causative factor and will enable him to direct treatment along constructive lines. Elimination of one of the channels of investigation often will lead to an incorrect approach to the problem and will relegate the diagnosis to that mysterious category of sciatica.

"To soothe the acute and stimulate the chronic" as stated by Downey¹ will result only in remissions of the symptoms. Every effort must be made to determine the causative factors, and treatment should be instituted in accordance with the findings.

Much has been written about the etiology of sciatica. Many who have written with enthusiasm have had to see, even in their lifetimes, that their explanation has become one among many and, in some instances, no explanation at all. However, this enthusiasm and desire to establish a cause has led to the better understanding of the condition and has, in

several instances, definitely established causes for sciatica. Sciatic pain, in itself, varies and the accompanying symptoms are rarely the same in any two patients. Study of the various combinations has led to the establishment of the different clinical syndromes and has rendered the accurate diagnosis of sciatica from an etiologic standpoint very difficult. Those who have seen and treated a large number of patients with sciatic pain have come to know that the cause usually originates in some factor which can be removed by the instigation of simple measures and that operative intervention is necessary only on occasions. To recognize these occasional cases and to apply the conservative measures or the operative procedures when they are indicated requires the best judgment and diagnostic acuity.

Considerable time should be spent in obtaining the information which the patient has for you, as much of value can be learned from the history. Has there been a previous injury? Has some stiffness in the spine been associated with the sciatic pain? Has the pain been helped or relieved by rest? What previous treatment has the patient had? From this one question much information can be obtained, as often patients have been treated elsewhere before they consulted you. They may well have had a period of rest or have worn a support without satisfactory results, the poor response being due to lack of complete bed rest or to improper selection of the appliance used. Inquiry should be made about the general health as the state of tone of the muscles and patency of the ligaments are logically the same as the other tissues of the body.

The physical examination of the patient should be done in the greatest detail. Have the patient remove all his clothes so that the general nutrition and the postural attitude can be analyzed. Palpate the bony prominences to determine any malalignment and the muscles and ligaments for areas of tenderness or abnormal thickening. Test the flexibility of the spine and the hip joints, paying especial attention to guarding of any segment and to localized areas of muscle spasm. In sacro-iliac conditions, the lumbar spine does not move freely when the patient is in the standing position because of the tension of the hamstrings, whereas motions are free and pain-

less if the motion in the lumbar spine is tested with the patient in the sitting position. The straight leg-raising test is helpful in the localization of strain, being more positive and usually unilateral in sacro-iliac conditions. In lumbosacral conditions, the test is less positive and is usually bilateral. The strength of the muscle groups should be tested, especially those supporting the spine and the lower extremities. Deterioration of the abdominal muscles weakens one of the important supporting structures of the spine and may be the cause of a chronic postural attitude. Weakness of a muscle group in an extremity or absence or inequality of the deep reflexes may indicate the necessity for a spinal puncture to reveal the diagnosis. The circumference of the calves and thighs should be measured to determine atrophy, and the length of the extremities should be checked routinely. The examination of other joints may reveal evidence of arthritic change and give help in the evaluation of the examination.

The routine examinations of the blood and urine should always be made. A sedimentation rate is often of value in pointing to any part which infection may play.

Roentgen examination of the lumbar spine and sacro-iliac joints should be made routinely, this including stereoscopic anteroposterior views, lateral views, and oblique views to visualize the foramina and articulations. The x-ray films should be studied with attention directed to anomalies, arthritic changes, evidence of narrowing of the intervertebral spaces, evidence of metastasis, old fractures, or any change in the anatomic alignment.

Patients with persistent sciatic pain which has not responded to rest and to which no definite cause can be attributed should have a lumbar puncture to help rule out any intraspinal lesion. The following case report supports this contention strongly.

The patient was a girl eighteen years of age whose complaints were that pain in the lower back and both legs had been present for fourteen months. She stated that she had fallen several years before while playing basket ball. Her back was injured then, but after several weeks she recovered completely. The onset of the pain had been gradual, and stiffness and aching in the back and legs had progressed. Her tonsils and appendix had been removed as possible foci of infection. Both the fascia lata had been devided without relief.

When first seen at the clinic, the examination revealed a poorly nourished patient with a very stiff lumbar spine. Both knee jerks and ankle jerks were absent, but no sensory disturbance or muscular weakness could be made out. Roentgen examination showed nothing other than a complete reversal of the lumbar curve (Fig. 66). Spinal puncture was unsuccessful between the second and third lumbar vertebrae. Puncture at the level between the first and second lumbar vertebrae revealed yellow fluid. Lipiodol introduced at this



Fig. 66.

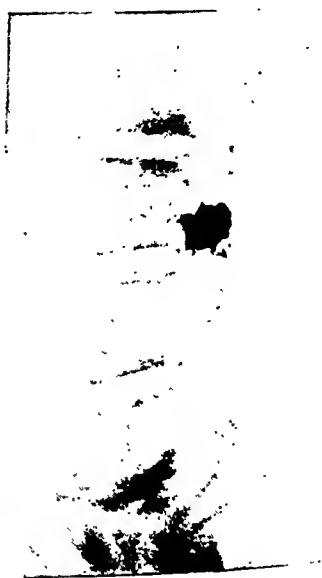


Fig. 67.

Fig. 66.—Lateral roentgenogram showing reversal of the lumbar physiological curve in a case of intraspinal tumor.

Fig. 67.—Lateral roentgenogram of case shown in Fig. 66. This was made after the introduction of lipiodol and demonstrates arrest of the lipiodol adjacent to the second lumbar vertebra.

level did not descend below the second lumbar vertebra (Fig. 67). Laminectomy in the second, third, fourth, and fifth lumbar regions was done, and the spinal canal below the second lumbar vertebra was found to be filled with a friable type of tumor tissue which was diagnosed microscopically as an ependymoma.

When, after thorough study, the diagnosis of chronic lumbosacral strain, sacro-iliac strain, lumbar myositis or fasciitis is made, a period of bed rest of two to three weeks is advised. Boards are routinely placed under the mattress as is light trac-

adhesions about the nerve sheaths. Under local anesthesia, an ordinary spinal puncture needle is introduced into the sacral canal. Fifty to 80 cc. of warm normal saline solution is then introduced slowly into the epidural space. Often there is rather marked relief from the sciatic pain. In cases with herniation of the nucleus pulposus, this procedure increases the pain and is used as a diagnostic measure.

There are a number of patients with sciatica, especially in the older age groups, in whom the roentgen examination shows little other than narrowing of the lumbosacral intervertebral cartilage. Williams³ has written on this subject and has given a rather logical explanation for the sciatic pain. As the disk becomes narrowed, there is a settling with narrowing of the fifth lumbar foramen which causes pressure or irritation of the fifth nerve. There is usually an increase in the lumbar lordosis. I have seen several such cases that have responded well to bracing and restoration of the normal mechanics of the lumbar region.

The recognition of herniation of the nucleus pulposus following injuries of the intervertebral disk has added a very definite pathologic condition as a cause of severe sciatica. This condition has been recognized for a number of years but attention has been drawn to it through the writings of Mixter and Barr⁴ and Hampton and Robinson.⁵ The condition is not a common one but has been shown to be more common than was previously thought, and it must always be considered as a possible explanation for severe sciatic pain. Clinically, the condition simulates the ordinary sciatica of chronic lumbar strain or fasciitis. There is usually a history of a previous injury, either recent or remote. This condition is usually seen in young and middle-aged men. The herniation most commonly occurs between the fourth and fifth lumbar vertebrae and next in frequency between the fifth lumbar vertebra and the sacrum. The pain is generally referred to the lateral aspect of the calf and is severe. The lumbar spine is guarded and the lumbar physiologic curve is reversed. There is tenderness over the ligaments and muscles due to the muscle spasm. There may be some weakness of the muscle groups but often the neurologic findings are confined to an absent tendo-achilles reflex. A narrow intervertebral space suggests that a herniation

of the intervertebral disk may account for the pain. Poor response to absolute bed rest may also be suggestive of this condition and would be an indication for further study by lumbar puncture. Lumbar puncture should be done low, and fluid should be obtained from the region of the suspected herniation. In most instances there is no evidence of block but fluid withdrawn from this region will usually show an elevated protein if a herniation exists. A determination of



Fig. 68.



Fig. 69.

FIG 68—Anteroposterior roentgenogram showing deformity in the lipiodol column in herniation of the nucleus pulposus at the level of the fifth lumbar vertebra.

FIG 69—Lateral roentgenogram showing narrowing of the fifth lumbar interspace and deformity in the lipiodol column due to herniation of the nucleus pulposus at this level.

more than 40 mg. per 100 cc. should be considered as a definite elevation. Persistent pain and elevation of the protein content of the spinal fluid are indications for study with lipiodol. A definite deformity in the lipiodol column is seen when a herniation exists. If the herniation is demonstrated, laminectomy is indicated and removal of the herniated nucleus offers the solution for the sciatic pain due to this cause.

The roentgenograms (Figs. 68, 69) show the deformity in

the lipiodol column due to a herniation of the nucleus pulposus at the level of the lumbosacral junction. This was the case of a fifty-year-old woman who had had intermittent attacks of sciatica during the preceding twenty years. The last attack had been present for nine weeks and had not responded to rest. An epidural injection of 60 cc. of normal saline solution made the pain worse. A laminectomy revealed the herniation of the

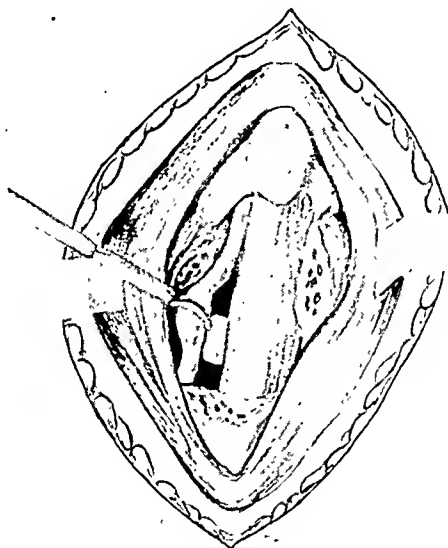


Fig. 70.—Drawing made at the time of operation on the case shown in Figs. 68 and 69. The herniation of the nucleus pulposus produced pressure on the fifth nerve

nucleus pulposus at the lumbosacral junction with pressure on the fifth nerve root (Fig. 70).

In summarizing I would like to emphasize the necessity for a thorough investigation in the presence of sciatic pain as the efficiency of the treatment will depend on establishing an accurate diagnosis, and to stress the fact that several conditions may give rise to the symptom—sciatica.

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SOME OBSERVATIONS ON TOXIC PSYCHOSES

JOHN TUCKER

THE psychic reactions which result from acute and chronic disease and from the prolonged use of sedative or narcotic drugs present a common problem in the practice of medicine. If the patient is constitutionally unstable, he will react unfavorably to a lesser degree of fever and toxemia. In a relatively mild infectious disease or following the use of comparatively small amounts of alcohol or bromides, he may manifest discernible changes in personality. It is important for practicing physicians to realize that all mild mental changes may not be the early symptoms of a psychoneurosis, manic-depressive psychosis, or schizophrenia, but rather that they may indicate an intolerance to toxins that come from within or from without. Unfortunately, one cannot always differentiate between functional and organic nervous diseases without a careful diagnostic study of the patient. It is with this fact in mind that some of our experiences in the study of these psychic states are recorded.

The textbooks on psychiatry inform us that, for practical purposes, the toxic psychoses can be divided into the endogenous and exogenous types. The endogenous variety deals with the peculiar nervous and mental reactions incident to fever, infection, and the mental derangements due to disturbances in the organs of metabolism and excretion. Among these are nervous responses to the high fever of pneumonia, acute rheumatic fever, and chronic tuberculosis, or to many afebrile ailments such as diabetes, uremia, and cardiovascular disease. In the exogenous toxemias, we think of the abnormal mental effects of the heavy metals such as mercury, arsenic, and lead, or of the reactions to acute and chronic alcoholism, bromides, barbiturates, and finally to the demoralizing effects of the habitual use of narcotics. In both of these types of toxemias,

the endogenous and the exogenous, we find many common symptoms. The range of psychic response is from that of deepest depression to the disturbing manifestations of acute delirium. In some cases, we meet with a dulling of consciousness, a mild confusion, or simple disorientation. In acute febrile conditions, this dreamy state may persist or it may rise rapidly to acute delirium with marked restlessness and visual and auditory hallucinosis. As a rule, this change parallels the degree of hyperthermia and toxemia. A similar condition may develop in those individuals who, though not disturbed by infection or fever, are peculiarly susceptible to sedative drugs. Several experiences along this line seem to emphasize the mental effects that may be brought about by the uncontrolled use of bromides and barbiturates.

A young man, about thirty years of age, was brought to the clinic by his sister. His chief complaints were of marked fatigue, agitation, and alternating short periods of somnolence throughout the day. Among his complaints were morbid thoughts of suicide, failure of memory, and a blurring of vision which at times was accompanied by diplopia. Physical examination gave normal findings except for a condition of general body relaxation, sluggish reflexes, and an inclination to lapse into short periods of sleep. In the historical review of this case, it was established that the patient had suffered with a rather severe infection of the upper respiratory tract a week or ten days prior to the onset of his psychic upset. However, to his best knowledge, there had been no definite febrile reaction. At this point in the examination, we were inclined to consider the possibility that he might be afflicted with the early stage of lethargic encephalitis. However, further observations were quite illuminating. Responding to direct questions, his sister informed us that very recently he had been forced into bankruptcy, his automobile agency having failed to weather the storm of the depression. The humiliation and worry had produced anorexia and insomnia, for which he resorted to the use of bromides, 15 grains having been taken three or four times a day for several weeks. In spite of this, his agitation seemed to increase and, while he became more and more fatigued, he could not secure the oblivion of peaceful sleep. At this point, our interest was awakened to the possibility that he was suffering with chronic bromidism. It is true that he did not have a cutaneous rash although he had taken several hundred grains of bromide over a period of three weeks. Fortunately, he responded very rapidly to elimination therapy. He was given 15 grains of sodium chloride by mouth four times a day, intravenous injections of normal saline solution, 1000 cc. twice a day, and additional fluids by mouth and saline catharsis. In three days, he had lost his agitation and fatigue and had established a normal sleep rhythm.

A second problem of similar character occurred in a woman, fifty years of age, who had carried heavy responsibilities as superintendent of a hospital for

more than a decade. During her menopause, minor nervous symptoms developed and about six months before admission to the hospital she began to take bromides quite regularly. These enabled her to secure sleep and relaxation as well as to furnish sedation during the day. In spite of this medication, she began again to be nervous and, as she increased the dose of bromide, vagaries in her mental state developed. At times, she would forget to perform certain regular duties and she became incoherent and agitated with any unusual hospital situation until she was unable to carry any responsibility. After consultation with her staff physicians, she was given various other sedatives, none of which seemed to produce adequate relaxation. When she consulted us, it was evident that she was in a state of hypomania. Careful questioning of her attending nurse gave us the clue to her previous medical treatment. The physical examination showed no evidence of organic disease of the central nervous system. We established therapeutic measures similar to those employed in the previously mentioned case. After treatment for five days she was entirely relieved of her mental symptoms. By this time, the excess of bromide ion had been eliminated from the body.

A third case involved the use of a barhital derivative. The patient was a woman, thirty-five years of age, who in her normal state had exhibited the manic and depressive variations of cyclothymia. However, this emotional instability had not interfered seriously with her ability to maintain her responsibility as a wife and mother. During a period of about two months preceding our examination, she had found it necessary to use a coal-tar preparation to induce sleep. Shortly before admission to the hospital acute delirium developed. She heard voices at her bedside and she was in communication with heavenly beings. On one occasion, she escaped into an adjoining room, singing psalms and exhorting the helpless patient to repent her ways. Her delirium was of sufficient violence to require restraint. In her physical survey, such as could be carried out, she was found to have no organic disease. By the use of hot packs, mild catharsis, saline given intravenously and forced fluids by mouth, she gradually subsided to a normal mental tempo. It was our opinion, after due consideration, that she had been suffering from the toxic effects of chronic barbital poisoning. While her personality was fundamentally of the cyclothymic type, this severe manic reaction was rapid in onset and coincided with the use of rather large amounts of this particular sedative.

The phenomenon of drug hypersensitivity is not uncommon in clinical experience. We are curious to know just how the body reacts and yet, at the present time, the mechanism of drug intoxication is not understood. In some of the cases of acute delirium, it would seem that the cerebral irritation takes place at the cortical level. In other instances in which the major symptoms relate to muscular incoordination, vasomotor and respiratory disturbances, the drug may act directly on the brain stem. This would pertain particularly to the basal nuclei, the red nucleus, and the hypothalamus or diencephalon.

Some authors have suggested that bromides inhibit the cortical cells while the barbiturates have a selective effect on the subcortical centers lodged in the midbrain and pons. In toxic doses or with smaller amounts in susceptible individuals, the effect may be irritative rather than sedative in character. On the other hand, except in hypersensitive people, the action may not be selective but rather a matter of the degree of sedation. The toxic effect may show itself primarily in the cortex or again in the subcortical centers. Which area may be affected first is dependent on many unknown factors relating to absorption, circulation, metabolism, excretion, endocrine activity, and the important matter of tissue sensitivity.

A much more commonly used exogenous toxin is ethyl alcohol. The present flair for cocktail parties, especially among young people who have not as yet reached the age of stability and discretion, has not been devoid of its harmful effects. Alcohol has a peculiar affinity for nerve tissue. Autopsy reports following deaths from acute alcoholism reveal damage to the cortical cells of the brain. From a clinical standpoint, we know that severe mental and moral deterioration does occur in chronic alcoholics. It is reasonable to assume that smaller quantities of this drug may have equally unfavorable effects on young people during the unstable period of adolescence and youth, and especially in those who have a psychoneurotic makeup. The use of alcohol as a means of escape from reality may be especially dangerous during the formative periods of life. After forty years of age its moderate use is probably beneficial; however, to secure the best results, it should be used temperately. According to E. A. Strecker,¹ chronic alcoholism accounts for from 5 to 10 per cent of all mental disease. He states that "even in moderate doses, alcohol lessens motor activity, increases reflexes, diminishes physical strength, lowers the fatigue point, interferes with the clarity of ideation, impairs capacity for judgment and mental work, and interferes with the sharpness of memory and the stability of the emotions." Recent investigations have shown that the habitual use of excessive amounts of alcohol may not only damage nerve tissue but it also interferes with the absorp-

¹Strecker, E. A.: *The Diseases and Abnormalities of the Mind*, Osler's Modern Medicine, vol. 6, p. 902, Philadelphia, Lea and Febiger, 1928.

tion of proper amounts of the essential vitamins. Likewise, the habitual drinker may subsist over a period of years on an inadequate diet. It is easy for him to substitute a scotch and soda for a noon lunch and to eat excessive amounts of carbohydrates at his regular meals. A certain number of these *bon vivants* may develop the mental, emotional, and peripheral nerve manifestations of acute or chronic pellagra. With this, the cutaneous changes on the exposed parts may add to the disability. The severe mental changes may include hallucinosis, delusional states, impairment of memory with confabulation as occurs in Korsakoff's psychosis, and even a progressive type of paranoid reaction. In young people, psychoneurotic reactions of the neurasthenic or hysterical form are fairly common. Fortunately, however, these minor symptoms subside fairly promptly after the withdrawal of alcohol and the institution of hydrotherapy, sweats, and elimination through the kidneys and bowels. Except in severe alcoholic intoxication, such as delirium tremens, it is fairly easy to treat the patient. The major therapeutic problem is educational. As a rule, in due time, the individual again meets the difficult problems of life with alcohol rather than with fortitude.

The diagnostic problem is much more difficult in the mental and emotional derangements of endogenous toxic states. It must be realized that every somatic disease carries with it mental and emotional reactions as well as physical expressions. While much of the derangement may be due to the direct effect of the bacterial endotoxins and exotoxins on nervous, glandular, and other tissues, a certain modicum of the difficulty is social and economic. In any chronic disease state, the patient must make certain mental and emotional adjustments. His family may suffer from want of the ordinary necessities of life, his job may be lost, and the cost of nursing may be a great burden to the family. It is natural for an invalid to become a psychoneurotic. The diagnostic problem is twofold—we must determine the influence of infection and disease, and then we must evaluate the chronic invalid reaction of the patient. Is he well balanced or has he his disease plus neurasthenia? In many instances, these two states cannot be clearly separated. The answer rests with the care used in the clinical examination.

In history taking, the patient should be allowed to tell his story in his own way. He should describe his chief complaints and symptoms in chronologic order. During this recital, the physician can, to some extent, evaluate the patient's personality. With some years of experience behind him, the family physician or consultant can readily detect signs of nervous instability. He may discern hypomanic or melancholic tendencies. The personality may show disorganization with paranoid trends manifested by feelings of suspicion and ideas of persecution. The physician is also interested in all historical data that may point to chronic infectious states such as tuberculosis, acute and chronic rheumatism, and encephalitis. The story may suggest that the patient has diabetes, chronic uremia, cardiovascular disease, anemia, or arteriosclerosis. The taking of this preliminary history should be unhurried. The physical examination should be thorough, with a careful study by means of inspection, palpation and percussion. Examination of the eyes, teeth, rectum, and prostate gland should not be neglected. Likewise, the temperature, pulse, and blood pressure should be recorded. In the laboratory data, certain tests should be made routinely; these include urinalysis, blood counts, blood sugar, and Wassermann reaction. In certain cases, we are unable to complete the examination without resorting to special studies of the blood for estimation of calcium and phosphorus, nonprotein nitrogen, uric acid, blood proteins, or many other clinical tests. Likewise, roentgen examination of the lungs and genito-urinary and gastro-intestinal tracts may reveal evidence of infection or neoplastic disease. A determination of the basal metabolic rate is of much value when the emotional level is above or below normal range. Such a study has a double value—it not only furnishes important diagnostic data, but it also serves to convince the nervous patient that at least someone is making a careful study of his problem. He is now in a proper psychologic mood to add important details to his story. Let us assume that the examination so far has shown normal findings. At this point, an additional half hour in history-taking will prove most valuable. If the patient is a newcomer to your office, he has had an opportunity to become acquainted and time to think about some of the questions brought out earlier in the diagnostic survey. It is particularly

important to hear more of his family life, his sex history, and the problems of his early childhood. Very often, one finds out that there is incompatibility between the husband and wife, and the in-laws are upsetting the family tranquillity, or that an invalid parent is being cared for in the home. There are so many different angles to these problems that one can only suggest a few of the common factors that may throw the patient from a normal to an abnormal emotional status. His severe fatigue and weight loss may be brought about by the combined effects of disease and worry. The conscientious doctor is compelled to function both as an advisor and a physician.

When the patient is in normal health and if he is living a temperate life in all respects, he is usually fairly stable in his emotional life. When he manifests excessive irritability or fatigue day after day, he is either working too hard, he is greatly worried, or he has organic disease. Before middle life, the more common abnormalities are produced by endocrine imbalances, acute or chronic infections, and blood dyscrasias. In the later years, we search for degenerative diseases such as arteriosclerosis, cardiovascular-renal disease, diabetes, hypochromic and pernicious anemia, and disturbances incident to the climacteric. One elderly patient, eighty-two years of age, came to the clinic complaining of fatigue, insomnia, loss of memory, and anorexia. His wife stated that she knew that his symptoms were due to old age but that, to humor him, she brought him in for examination. The local physician had made a diagnosis of senile dementia. The important physical findings were glossitis, paresthesia in the hands and feet, loss of vibratory sense in the toes, and a blood picture of a severe anemia accompanied by macrocytosis and high color index. While it was evident that the patient had severe generalized arteriosclerosis, it was likewise apparent that he was suffering with pernicious anemia. When he was put on a high vitamin diet with plenty of cooked liver and also intramuscular injections of liver extract semiweekly, he was restored to a satisfactory physical and mental state in six weeks' time.

One must recognize the fact that elderly people can have diseases of infectious and metabolic origin as well as degenerative vascular changes. Prostatic hypertrophy with associated chronic uremia often causes mental changes. Likewise, we

must not forget that syphilis of the central nervous system is often overlooked. The sudden onset of neurasthenia in middle life without apparent precipitating factors may herald the early symptoms of general paresis. Not infrequently, the mental aberrations of elderly people will clear up after several abscessed teeth are removed or when a condition of masked hypothyroidism is treated with adequate doses of thyroid extract.

One may not be justified in classifying all these conditions as toxic states. However, the physical effects of these various diseases will serve to modify the psyche to such an extent that the patient is thought to be mildly or severely insane. One of the most enlightening aspects of modern medicine is the realization that most infectious diseases, while apparently localized in one organ or group of organs, have a general deleterious effect on the whole body. The nervous system is not immune to the toxins of pneumonia and rheumatic fever. In most instances, when toxic psychoses appear, they will respond to proper treatment of the underlying disease. When the careful family and personal history, as well as the objective physical and laboratory findings, fail to explain the mental and emotional changes, it is our duty to call in a competent psychiatrist. This should be done as early as possible after the symptoms appear. The specialist is better able to recommend or supervise the proper sanitarium treatment. He is trained to evaluate the early personality trends of the patient. He may be able to show that the acute or chronic infection or that the chemical intoxication has served to magnify an underlying mental disease. Thus manic-depressive psychosis or dementia praecox may graduate from an incipient to an active stage. Furthermore, many psychopathologic borderline conditions, such as the psychoneuroses, may respond to treatment if some constructive measures are instituted. Space does not permit discussion of the differential diagnosis between toxic and organic psychoses. A careful perusal of the standard textbooks on medicine and psychiatry will help in some degree to clarify the immediate problem. Every physician should take the time and trouble to familiarize himself with the common types of functional and organic mental disease. This knowledge will enable him to recognize the early deviations from a normal psychic state and will be of great value to the patient and his family.

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SYMPOSIUM ON NERVOUS AND MENTAL DISEASES

The following clinics are included in this Symposium:

Tracy J. Putnam: NEUROLOGIC EXAMINATION IN GENERAL PRACTICE.

Stanley Cobb and Neil T. McDermott: POSTOPERATIVE PSYCHOSIS.

H. Houston Merritt: THE DIAGNOSIS AND TREATMENT OF VASCULAR LESIONS
IN THE BRAIN.

Erich Lindemann: HYSTERIA AS A PROBLEM IN A GENERAL HOSPITAL.

Edwin M. Cole: DISABILITIES IN SPEAKING AND READING.

Philip Solomon: THE CAUSES, DIAGNOSIS, AND PROPER HANDLING OF COMA.

Madelaine R. Brown: DIAGNOSIS AND TREATMENT OF POLYNEURITIS.

David Young and William Beecher Scoville: PARANOID PSYCHOSIS IN NARCO-
LEPSY AND THE POSSIBLE DANGER OF BENZEDRINE TREATMENT.

Abraham Myerson: TRAUMATIC NEUROSES.

Leo Alexander: ELECTRICAL INJURIES TO THE CENTRAL NERVOUS SYSTEM.

Theodore J. C. von Storch: THE MIGRAINE SYNDROME.

Elmer C. Bartels: DIAGNOSIS AND TREATMENT OF MÉNIÈRE'S DISEASE.

CLINIC OF DR. TRACY J. PUTNAM

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NEUROLOGIC EXAMINATION IN GENERAL PRACTICE

The Procedures of Diagnosis.—The diagnosis of disease is attained—if at all—by one of four general methods. The first is recognition from past experience, from an impression of grouping of phenomena, as we recognize the face, voice and gait of a person. But this method, while the most frequently useful, is learned by practice alone. Moreover, it applies only to the relatively familiar; most of us can easily identify a friend, but may make distressing mistakes in placing acquaintances.

A second method is the recognition of a pathognomonic sign, as tubercle bacilli in the spinal fluid. But usually the sign must be searched for, after a tentative diagnosis reached by other means.

The third is the so-called “logical” or “deductive method,” and this is the one with which the present article chiefly deals. From a consideration of all the manifestations of a disease, we form a conception of the disordered physiology, hence of the anatomical disturbance, and so by inference of the pathologic changes and the etiology. Neurology offers unexcelled opportunities for such deductions, and a useful proficiency in them is not difficult to attain.

The fourth method is applicable only to psychiatric problems. It consists in attempting to put one's self in the patient's place, and feeling one's way into his mental processes. But it need not concern us further here.

The Essential Points of Neurologic Examination.—Many practitioners of medicine have the impression that the examination of the nervous system entails an elaborate technic,

and a knowledge of high sounding terms. This is not true. A brief examination of the nervous system can be made along with the general physical examination without undue trouble. This minimum examination should be a routine part of all physical examinations. If the findings of this examination are negative, there is very little likelihood of disease of the nervous system. On the other hand, if abnormalities are found, further examinations can be made.

The minimum examination can be summarized as follows: An inspection of the patient, gait, facies, etc., should be made. Also palpation of cranium and spine should be done. The cranial nerves can be rapidly examined by noting the size and shape of the pupils and their reaction to light, the eye movements, facial movements, rough hearing tests and examination of the tongue movements.

The motor system can be tested by testing the strength of grips, watching gait, inspecting muscles, and performing finger-to-nose test.

Sensory tests other than Romberg test are not necessary unless specific complaints or other findings indicate them.

The knee jerks, ankle jerks and plantar responses should be tested.

Several books dealing with methods of examination are available, of which perhaps the most complete and practical is that by Monrad-Krohn.¹ Most of them suffer from being encyclopedic. The present outline makes no pretense to thoroughness, but aims rather to be a guide to eliciting the information essential for a diagnosis with the least expenditure of time. The order of examination which it follows is the standard one.

General Examination of the Surface of the Body.—The practitioner needs less instruction on this point than do many neurologists. The skull and scalp should be palpated with care for irregularities or points of tenderness if intracranial disease is suspected. Tumors near the surface produce a local hyperesthesia. Those in the posterior fossa in particular are often accompanied by a soreness of the suboccipital muscles—not of the mastoid—and by pain on sharp flexion of the head.

Cranial Nerves.—*Olfactory.*—Evidence of any disturbance of the sense of smell is usually obtained by history. Ol-

faction may be tested by closing one of the patient's nostrils, and suddenly presenting any odorous substance—toothpaste, tobacco or the like—while the patient sniffs. It is of little value to test for *degrees* of loss of sense of smell. Ideal test odors are coffee and vanilla. Menthol is convenient to carry in the bag. Ether, ammonia, and vinegar, which are often used, act as stimulants to the trigeminal as well as to the first nerve. Unilateral anosmia should raise the suspicion of a tumor arising from the cribriform plate.

Optic.—Examination of the disks is of value in disclosing definite choking, atrophy, arteriosclerosis or retinitis. It is usually a mistake for most of us to be agitated over questionable or marginal changes. Mild grades of increased intracranial pressure are best measured by lumbar puncture; paling of the disk is of small significance unless accompanied by changes in the visual field.

Some record of visual acuity, as the ability to read large or small print, or recognition of fingers, should be part of every neurologic examination.

Gross field defects may be estimated by finger perimetry; that is, by having the patient close one eye and fix the other on the examiner's nose, and then signify when he sees the examiner's fingers moving in one quadrant after another. This is, however, an inefficient method of examining the central vision and size of blind spot, which is important in recognizing retrobulbar neuritis and similar conditions. If the eyegrounds are abnormal, or visual acuity reduced, an ophthalmologic consultation is in order.

Oculomotor, Trochlear, Abducens.—The method of testing the movements of the eye and reactions of the pupil is obvious. Nystagmus is usually considered to exist if there are more than three tiny jerks on extreme lateral or vertical fixation. Strabismus may be obvious, or almost impossible for the examiner to detect. It should be remembered that injury to the third nerve as a whole causes both dilation of the pupil and a limitation of movement of the bulb except for lateral rotation. Injury to the sixth makes complete abduction impossible. Injury to the fourth impairs the ability to look down and in.

Any deviation from these simple, obvious disabilities means that the lesion is in the myoneural junction (myasthenia, botu-

lism), orbit (in which case there should be local signs), or in the nuclear and supranuclear apparatus, which is too complicated to be described here. The disease entities of carotid aneurysm and progressive ophthalmoplegia should be considered in relation to obscure diseases of the oculomotor apparatus. Isolated, transient ocular paralyses are usually due to syphilis, multiple sclerosis, arteriosclerosis or encephalitis.

Trigeminal.—Irritation of or injury to the trigeminal nerve usually causes subjective disturbances of which the patient complains. The most delicate test for trigeminal sensation is to touch the cornea with a wisp of cotton. The use of a pin, brush, etc., for delimiting areas of hyperesthesia needs no description. Remember that the cervical segments come well up on the cheek, and are normally definitely less sensitive than the trigeminal area. The motor root of the fifth nerve may be tested by palpating the masseter as the patient bites. If the pterygoid is paralyzed, the patient is unable to move the jaw to the *opposite* side.

Facial.—Facial weakness is usually obvious, and the distinction between a peripheral palsy which involves the whole side of the face equally, and a palsy due to a cortical lesion which leaves the forehead relatively strong, is well known. Mild degrees of weakness (of the peripheral type) may often be detected by the force required to lift the closed lids. A weakness in voluntary movement due to cortical injury may be accompanied by an overactivity of the affected side on emotional expression, so that the question often comes up which side of the face is actually the one affected.

Auditory.—A simple routine test for hearing is to rub the thumb and forefingers beside the ear. If this trifling sound is heard, it is seldom necessary to go further. If any degree of deafness exists, a study should be made to determine whether its cause is in the middle ear or in the end-organ, nerve or medulla. If the middle ear is affected, sounds heard by bone conduction are relatively intensified. A tuning fork on the forehead or bridge of the nose is better heard in the deaf ear if the middle ear is chiefly involved, less well if the nerve is involved. If no tuning fork is at hand, a watch laid on the mastoid may serve for differentiation. Middle-ear deafness affects chiefly low notes, nerve deafness chiefly high ones, and

this can be determined by whispering or whistling. Be sure to inquire after tinnitus, if an acoustic tumor is suspected. None of the old standard tests compare in accuracy with the modern audiometer, but this is an expert's instrument.

Vestibular Function.—The concurrence of vertigo and of nystagmus is about the most definite sign of vestibular irritation easily elicited. Either existing alone is likely to be due to a central lesion. Loss of vestibular function can be demonstrated only by irrigation of the ears or similar tests which are best left to a neurologist or otologist.

The Ninth, Tenth and Eleventh Nerves.—For purposes of examination, these may be remembered as the nerves of swallowing and phonation. Disturbances in their function are usually mentioned spontaneously in the history, or are obvious in the patient's speech. Movements of the palate are, of course, easily observed. The pharyngeal reflexes may be elicited as a differential point between injuries of the bulbar nerves or centers, and damage (necessarily bilateral) to their higher connections.

The Twelfth Nerve.—Atrophy or paralysis of the tongue is easily observed. If atrophy is present, fibrillation should be carefully watched for.

Motor System.—Examination of the motor system in patients who do not have any complaint of muscular paralysis, resolves itself chiefly into an observation of the patient; the gait on entering the office, the facial expression, the voice, hands and the presence or absence of associated movements, or the presence of involuntary movements (chorea, athetosis or tremor).

The musculature of the upper and lower extremities and trunk should be given a brief inspection, especially attention being paid to nutrition of the small muscles of the hand and the muscles of the shoulder. Fibrillary twitching of these muscles should be searched for. These groups of muscles are the most apt to be involved in diseases of the spinal cord such as progressive muscular atrophy, syringomyelia, cervical rib, etc. Strength of the muscles of the upper extremity can be rapidly examined by testing the hand grips, flexion and extension of wrists, elbows and the movements of the shoulder joint. Muscle strength in the lower extremity can be determined by testing

flexion and extension movements of toes, ankle, knee and hip joints. The musculature of trunk and abdomen is tested by asking the patient to rise from prone to sitting position without using the arms to aid him.

The Deep Reflexes.—The standard deep reflexes to elicit are the biceps, the triceps, the radial periosteal and the knee and ankle jerks. It is not essential to undress the patient to obtain them.

The biceps jerk is elicited by pressing on the biceps tendon with the left thumb, and percussing the thumb. The triceps jerk is elicited by percussing the tendon just above the olecranon. Percussion of the head of the radius causes a slight contraction of the flexor muscles of the forearm which may spread to the biceps. These are all ordinarily sluggish responses.

The knee jerk is almost always livelier. The ankle jerk may be extremely sluggish in normal individuals. It is best elicited by causing the patient to kneel in a chair. Ankle clonus is, of course, merely a multiple repetition of the jerk.

If the knee and ankle jerks are difficult to obtain, reinforcement may be employed. The standard methods are to ask the patient to squeeze his hands together tightly, or to count backward from one hundred.

Significance of the Deep Reflexes.—The general rule is, that the deep reflexes are abolished or diminished by injury to either the sensory or the motor limb of the reflex arc, and are increased by injury to the pyramidal system. These are, however, exceptions to the rule. In certain conditions (for example syringomyelia and amyotrophic lateral sclerosis), atrophy of anterior horn cells may go on concurrently with injury to the tracts controlling them, and decrease and increase of reflexes may then alternate. In cases of sudden, widespread injury to the pyramidal tract (for example, complete transverse lesions of the cord or extensive damage to the motor cortex) reflex activity may be destroyed for a longer or shorter interval.

Other Important Reflexes.—The Babinski reflex has been called "the most important sign in neurology." It is produced by firmly dragging a semisharp object along the outer edge of the sole and across the ball of the foot. The response of a

normal person is a plantar flexion of the great toe. A positive (abnormal) response is a slight dorsiflexion of the great toe, a spreading of the other toes and a contraction of the tensor fasciae latae. The presence of this abnormal response is definite evidence of injury to the pyramidal tract.²

If the response is sluggish or indefinite, it may sometimes be clarified by bending the knee slightly. In a cold room, the feet may have to be warmed to a comfortable temperature. A rounded object, or the tip of a finger, may be more effective in extremely ticklish patients; or the stimulus may be applied to the flexor surface of the toe joints, instead of the sole. The Chaddock maneuver consists in scratching the lateral aspect of the foot; it sometimes produces a dorsiflexion of the great toe when the Babinski does not.

The only other one of the foot signs of real importance is the Oppenheim reflex, brought out by stroking the shin with the knuckles or with the handle of a hammer sufficiently hard to cause some pain. The responses are similar to those of the Babinski test, and it is occasionally positive when the Babinski is not, though on the whole less sensitive.

In a higher segment, the absence of the abdominal jerks may have much the same significance as the Babinski sign, except when the abdominal walls are exceptionally flabby.

The nearest approach to the Babinski type of reflex in the hands is the Hoffmann sign, elicited by snapping the nail of the middle finger with the palm of the patient downward and the fingers limp. The abnormal response is an adduction of thumb and forefinger, but usually there is no response, and occasionally a twitch of the thumb will occur in a normal subject.

Other Signs of Pyramidal Tract Defect.—If the patient is requested to hold his hands out in front of him with eyes closed, weakness of one of them may manifest itself by an abnormal position of the fingers or by a gradual droop of the limb in the course of a minute or two. If he places the hands closely palm to palm and attempts to spread the fingers as wide apart as possible, he can usually abduct the fingers on the normal side beyond those on the weakened side.

A similar phenomenon in the legs is brought out even more definitely by the Barré test. The patient lies on his face, and

holds both lower legs vertical. The hemiparetic extremity will gradually drop in a series of small steps, in a manner not observed with a peripheral lesion even of extreme degree.³ In case of doubt, examine the patient's shoes. A hemiplegic leg will wear the outer side of the toe long before the remainder of the sole.

Disturbances of Sensation.—A sharp pin (best a steel pin) in a throat stick is an accurate instrument for testing sensation. Neater still is a small camel's hair brush with a bit of rubber tube about it, which protects the pin when not in use. In testing for loss of sensation, always have the patient close his eyes, and always proceed from the anesthetic to the innervated area. A firm drag of the pin is sometimes more effective than successive pricks. If an area is actually anesthetic, it will endure a long series of blows with the pin in a single spot, which is far more noxious than a single deep one.

The sensation of light touch with cotton or brush is more difficult, for it demands more attention from the patient. It is best to have him *count* each time he feels a touch, or he may neglect to inform you.

Testing for vibration sense with a tuning fork of deep pitch is of importance in the study of mild degrees of damage to the spinal cord. A study of the patient's ability to detect small passive movements of the toes is of similar significance. (Hold the toe by the sides to avoid calling pressure-sense into play.)

It is rarely essential to determine the sensitivity to heat and cold, except when the question of syringomyelic dissociation arises. The ability to recognize objects placed in the hands should be tested in suspected disease of the parietal lobe.

Significance of Sensory Changes.—A sensory examination is only as good as the *entente* between subject and examiner. Fatigue, ill-will or ill-humor on the part of either vitiates its value. It is extremely easy to suggest the boundary of an area of hypesthesia to a patient, or even to suggest the hypesthesia itself. The common hemihypesthesia for pin prick, stopping exactly at the midline of both face and body, and occasionally accompanied by dimness of vision and deafness on the same side, is the mildest form of hysteria.

The areas of loss of sensation following peripheral nerve injury correspond to the anatomic distribution of the nerve:

pain is more affected than touch; there may be hyperesthesia as well. In polyneuritis, hypesthesia of a "glove and stocking" distribution is the rule, fading off toward the trunk. Presumably the longest nerve fibers are the most vulnerable. Such areas of sensory loss are easily confused with the hysterical anesthetics, also usually of the "glove and stocking" type. In general, the loss of feeling of hysterical origin is complete, ends abruptly at a joint, and is accompanied by a contracture, weakness or tremor. But a differentiation is only to be made by considering the case as a whole. The coexistence of hypesthesia of the hands and feet with evidence of disease of the spinal cord (increased reflexes, Babinski's sign) is suggestive of a myelopathy resulting from deficiency disease such as pernicious anemia or pellagra.

The loss of sensation which results from a local lesion (for example a tumor) of the cord can usually be interpreted by consulting a standard diagram of the tracts.

The disturbances of sensation resulting from cerebral lesions form a complicated group. In general, loss of the sense of pain is rare, though there may be subjective numbness. The ability to recognize objects or fabrics by feeling, to localize pin prick or to recognize weights may be impaired.

Disturbances of Speech.—The subject of aphasia is as difficult as one cares to make it. Obviously, there is a distinction between an inability to coordinate the muscles of phonation (dysarthria) and an inability to understand speech, form concepts and express them.

The distinction between sensory and motor aphasia is not of great practical importance. When one exists, the other can usually be detected also.

The Mental Status.—If there is any question of loss of memory or alteration in personality, some inquiry should be devoted to its precise nature. Often the best record is a simple account of any incidents in the patient's life which appear unusual. Memory for events usually comes out in the course of history taking. A simple test for retention is to get the patient to repeat numbers. A normal individual should be able to retain a number of eight different digits, and should be able to repeat backward one of six digits. Such simple inquiries as who is President, who was the one before him and

the one before that will often bring out concrete evidence of loss of memory or observation.

Other obvious tests consist in giving the patient simple arithmetical problems or reading to him a few paragraphs from the daily paper, and asking him to give a summary of them.

One need not be a psychiatrist to make brief notes on mood, approachability, orientation for time and space, insight, and evidences of illusions, delusions or hallucinations.

Disturbances of Equilibrium and Coordination.—There is a fundamental distinction between the ataxia due to loss of position sense such as tabes, the disturbance of equilibrium produced by disease of the labyrinth or its central connections, and the disturbance of coordination of muscle groups produced by the cerebellum itself. Of course, they may coexist, but they should be tested for separately. True ataxia is shown by a loss of vibration and joint sense and by the tendency to fall (not merely to wobble) in standing with heels and toes together and eyes closed. Injury to the vestibular system gives rise to such symptoms as nystagmus, dizziness, nausea and asymmetry of stance or gait. Loss of cerebellar control produces the "decomposition of movement" or intention tremor, well brought out when the patient attempts to put the finger on the nose or the heel on the opposite shin with the eyes closed. Rapid alternating movements, as patting the knee, are impaired and the patient walks with a wide base and long steps. There is usually a diminished muscle tonus.

It should not be forgotten that disease of the brain itself—especially the frontal lobe—may produce disorders of coordination and nystagmus. They are, however, rarely pronounced in comparison to the severity of the disease as a whole as in disease of the cerebellum and medulla.

The Diagnosis of Disease of the Spinal Cord.—The neurologic signs of injury to the pyramidal tract are essentially the same, no matter where the tract is injured. But there are other descending (motor) tracts which are usually damaged in disease of the spinal cord, but not in disease of the cortex. If they are left intact (for example, in a hemiplegia from a capsular hemorrhage), a certain amount of crude voluntary movement is eventually established. If all the descending motor pathways (extrapyramidal as well as pyramidal) are about

equally injured but not destroyed, accurate control of the affected limbs may be possible, but hampered by the disproportionate spasticity. A complete destruction of all descending pathways leads to complete paralysis, and such hyper-reflectivity that a brush or a tap on the paralyzed leg may set all of the isolated segments into contraction, with voiding of urine and emptying of bowel.

Milder degrees of the special intrinsic activity of the spinal cord may often be demonstrated by a sharp pinch of the instep on the affected side. If there is even a slight interference with extrapyramidal as well as pyramidal pathways, the leg gives a sudden involuntary jerk, and the toes fan out as in the Babinski reflex. This sign is practically never positive if the disease is above the spinal cord.

The location of a local lesion of the spinal cord is most accurately studied by the level of loss of sensation (pin prick usually gives the most accurate results). Sometimes a tuning fork placed on the spines of the vertebrae in succession will reveal a definite change in sensation at one point. A line scratched on the skin may show a level of vasomotor hyperactivity. If a definite sensory level is demonstrated, the diagnosis of tumor is strongly suggested.

The presence of an expanding lesion or pressure upon the cord is suggested by local pain or tenderness elicited by scratching the skin or pounding the spines. Limitation of motion may sometimes be observed. Intrinsic disease of the spinal cord is apt to impair the control of the bladder and anal reflex relatively early, tumor relatively late. x-Ray evidence of the presence of tumor is disappointing, but tuberculosis and other deformities of the spine should be searched for.

The use of lumbar puncture, with careful studies of the pressure, dynamic and the protein content of the fluid, is indicated in all forms of disease of the cord. Injection of radiopaque oils and combined cisternal-lumbar punctures should be left to experts.

The Examination of a Patient in Coma.—Examination of a comatose patient presents special problems.⁵ The *depth* of coma throws little light on its cause. The history may reveal at once the source of the coma, but it should not be forgotten that two causes may coexist. A hemiplegia may be

detected by spontaneous movements of only one side or by the puffing out of a relaxed cheek in respiration, or by a difference in the promptness with which the arms fall when simultaneously raised and then dropped. Reflexes may or may not be obtainable. Pain responses may sometimes be obtained, for example by pressure on the supra-orbital nerve, or pricking the sole of the foot and may give indication of unilateral or localized weakness. Stiffness of the neck may be an indication of meningitis or subarachnoid hemorrhage.

Obviously the odor of the breath should be observed, the color of the mucous membranes and the type of respiration. The "soft eyeball" of diabetic coma should be remembered. A urine specimen must be obtained and examined (but in this connection it should be recalled that other conditions besides diabetes may cause glycosuria and acetonuria). Studies of blood chemistry are to be remembered.

A lumbar puncture is indicated in practically all cases, unless the diagnosis is obvious without it, or the patient's condition does not permit. The manifestations of meningitis, hemorrhage, or increased pressure from tumor are obvious.

In most localities, alcoholic and other intoxications are the most common cause of coma with trauma and cerebral vascular accident in the second and third places. Epilepsy, pneumonia, diabetes, meningitis, cardiac decompensation, neurosyphilis, uremia and eclampsia should also come at once to mind, approximately in the order named. The rarer causes are too numerous to mention.

Lumbar Puncture.—The interpretation of the results of lumbar puncture is a large study in itself, and the reader should refer to special articles or books on the subject.^{6, 7} In brief, lumbar puncture is unequivocally indicated in suspected cases of meningitis, syphilis, encephalitis, spinal cord tumor, myelitis and head injury. It is contraindicated, unless certain precautions are followed, if an intracranial tumor with increased pressure appears likely. In all cases, the puncture should be performed under local anesthesia in the recumbent posture, and the pressure measured with the patient relaxed. A test of the dynamics by pressure on the jugulars is particularly important in disease of the spinal cord. A cell count should be performed at once, and a sample of fluid sent for a Wassermann

test. A determination of total protein is the next most important test, and a determination of sugar if the cell count is elevated. A gold sol curve is often helpful in puzzling cases.

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POSTOPERATIVE PSYCHOSIS¹

DURING the last year we have seen 16 cases of postoperative psychosis that were not suffering from the usual delirium. Four typical cases are here briefly reported because it seems to us that they show a type of psychosis frequently seen in general surgical practice, but as yet are not adequately described or understood. They are quite different from the delirious reactions with which they are generally confused. The prognosis is good if proper treatment is promptly instituted. By an early diagnosis both the patient and the family may be spared much anxiety and trouble. Ebaugh² has discussed psychiatric complications in surgery in a comprehensive way and gives a bibliography of the subject.

Case I.—A Frenchwoman, aged thirty-eight.

Advice as to diagnosis and treatment was requested by the surgical service. Neurologic examination showed nothing abnormal except hyperactive reflexes. She has been operated on for gallbladder disease on November 30th. Following operation she had a moderate amount of morphine once or twice daily. On December 4th she became noisy, saying that she was in Heaven and that she saw her children with her. On the morning of December 5th she described a half-sleep state in which she had seen her children "as plain as day in Heaven"; she believed it was probably true and not a dream. She was well oriented for time and place. Later in the day when rounds

¹ This work was aided by a grant from the Josiah Macy, Jr., Foundation.

² Ebaugh, F. G.: *Bull. Am. Col. Surgeons*, 22: 153, 1937.

were being made by the visiting surgeon, she held the sheet over her face, seemed afraid, and would not look in the corner of the room; she said her father had told her not to. She saw heaven over in the corner of her room, and there were angels around her. She mistook the resident psychiatrist for a certain friend of hers and held his hand amorously. Later she started to get out of bed, so it became necessary to move her immediately to the psychiatric ward. Here she was put in a single room with a special nurse. On December 7th she was still seeing the bright light and "lots of angels in the room"; she thought the nurse was an angel, and said she had wings, but would not tell the doctor just where they were. She smiled and laughed a good deal. She gradually improved on the psychiatric ward and was discharged December 15th to her home. On January 12th she was seen in the out-patient department and seemed perfectly well.

Case II.—A thirty-five-year-old Irish woman.

Consultation was requested because of peculiar ideas expressed by the patient. Neurologic examination showed slight arteriosclerosis and hypertension, the blood pressure being 230/140. There were no other abnormalities found.

The patient was born in Ireland and came to this country at the time of her marriage eleven years ago. She has three children who are well; her husband died of pneumonia two years ago and at his death the patient was quite upset. For the past five years, the patient has had headaches which have become severe in the past year, accompanied by dizzy spells, nose bleeds, and occasional swelling of the ankles. She was admitted to the medical service. A diagnosis of malignant hypertension was made. She was transferred to the surgical service for sympathectomy, which was performed on June 14th under gas oxygen and ether. Postoperative course was uneventful with normal temperature on the fourth day. She received little medication and was getting on so well that it was planned to perform a sympathectomy on the other side within a few days. The development of her psychotic symptoms, however, made this inadvisable.

She was seen lying quietly in bed. She told a vague story about nurses laughing and talking about her, of doctors taking

pictures of her, of a plan the doctors had to strap her down and not let her go home. She also said that her brother was outside, that doctors had him strapped down and would not let him come in and see her. She believed that the night before, someone was putting electricity through her. She was oriented for place; knew the month and year, but missed the exact date by about three days, and changed her answers concerning the day of the week. She knew the doctors and was not confused as to her own identity.

Recommendation: Transfer to psychiatric ward. Give as little medication as possible.

June 23rd. Since transfer to the psychiatric ward, she has been perfectly oriented on all occasions. At first she insisted that her children were being held in the hospital, or were being driven around the hospital in an ambulance. She often heard people talking about her, heard her children's voices and the nurses heard her talking to herself. Two days ago her brother visited for the first time. She seemed to improve after that. This morning she is perfectly well and says she does not hear the voices any more nor does she have her peculiar ideas. She said that they must have been imaginary and caused by her nervousness after the operation.

Case III.—An Italian woman of forty-eight.

Consultation was requested because patient was disturbing the surgical ward. The patient had repair of abdominal hernia on May 18th. On May 21st she said she wanted to go home. Next morning she became noisy and by evening was greatly excited. She refused to be examined and was interviewed in a dark ward. She was screaming that she wanted to go home to see her daughter and that she wanted an Italian doctor.

She was moved immediately to the psychiatric ward, where she was put in a single room with special nurses. May 23rd she continued to be noisy. On the 24th, after her daughter visited her, she became more cooperative and allowed the examiner to find that she was well oriented, and that the neurologic examination was negative. She told her daughter that she had heard people here calling her bad names and other people accusing her of prostitution; she said that the doctors here were going to kill her.

On May 27th she was quieter but still seemed apprehensive at times. The daughter thought that she could care for the patient at home, so we reluctantly discharged her "against advice." A follow-up visit showed that no mistake had been made in letting her go. She was cared for by a doctor who spoke her language, and her daughters were with her continuously. She improved steadily and was well and able to work in July.

Case IV.—A fifty-three-year-old Portuguese woman.

The orthopedic service asked for consultation because of the behavior problem. A satisfactory neurologic examination could not be done because the patient was restrained in bed by orthopedic apparatus.

Three weeks ago she fell off a wall and broke her leg. She was brought to the hospital, the bone was set and the patient was put in traction. Everything was going well until December 4th, when the patient became restless and felt that the nurses did not want to give her bed pans. On December 6th she began to shout and was moved into a single room. Conversation with the patient, through the interpretation of the patient's twenty-three-year-old daughter, revealed the following: The patient has been well. There has been no difficulty like this until recently in the hospital. She felt she could not pronounce "bed pan" correctly. She then said that when she asked for the bed pan other patients noticed her and made fun of her, as did the nurses. This morning she could hear voices shouting "bed pan, bed pan, bed pan." She does not hear the voices now. She seems fearful and says "I'm afraid." She fears that something will hurt her, that the medicine may hurt her, that the doctors will strap her down. She pleads, "Doctor, don't hurt me."

Her memory seems good and her orientation is accurate, *i. e.*, she recognizes the doctor and realizes her own identity. She knows that this is a hospital, but does not know its name; she knows it is in Boston. She does not know the date, but knows she has been in the hospital three weeks (which is correct). Her mood is somewhat depressed. In brief, she has a noisy, agitated, depressed state with delusions that she had done wrong and is to be punished.

- Recommendations: (1) Keep a close watch on the patient. (2) Use paraldehyde as the only sedative. (3) Have the

CASE NO. 30265		BEHAVIOR SHEET																			SLEEP GRAPH													
1936	1937	PROXIED	VULGAR	COMBATIVE	AGITATED	IRRITABLE	MOODY	RESTLESS	TALKATIVE	SMILING	OCCUPIED	QUIET	BROODING	WEEPING	FEARFUL	CONFUSED	MUTE	SUCIDAL	RESISTIVE	PARALDEHYDE GRAMS	PM							AM						
																					8	9	10	11	12	1	2	3	4	5	6	7		
DEC	13				X	X	X	X	X					X							3				X	X	X	X	X	X	X	X		
	14		X		X	X	X	X	X					X							3				X	X	X	X	X	X	X	X		
	15		X		X	X	X	X	X					X							3				X	X	X	X	X	X	X	X		
	16				X	X	X	X	X					X											X	X	X	X	X	X	X	X		
	17		X		X	X	X	X	X					X											X	X	X	X	X	X	X	X		
	18				X									X							3				X	X	X	X	X	X	X	X		
	19				X	X	X	X	X					X											X	X	X	X	X	X	X	X		
	20				X	X								X										X	X	X	X	X	X	X	X	X		
	21									X				X							3				X	X	X	X	X	X	X	X		
	22									X				X											X	X	X	X	X	X	X	X		
	23									X				X							3				X	X	X	X	X	X	X	X		
	24									X				X											X	X	X	X	X	X	X	X		
	25									X				X											X	X	X	X	X	X	X	X		
	26									X				X											X	X	X	X	X	X	X	X		
	27									X				X							3				X	X	X	X	X	X	X	X		
	28									X				X											X	X	X	X	X	X	X	X		
	29									X				X							3				X	X	X	X	X	X	X	X		
	30									X				X											X	X	X	X	X	X	X	X		
JAN	1				X				X					X							3				X	X	X	X	X	X	X	X		
	2				X									X							3				X	X	X	X	X	X	X	X		
	3				X									X											X	X	X	X	X	X	X	X		
	4													X							3				X	X	X	X	X	X	X	X		
	5				X									X											X	X	X	X	X	X	X	X		
	6													X							3				X	X	X	X	X	X	X	X		
	7													X											X	X	X	X	X	X	X	X		
	8													X							3				X	X	X	X	X	X	X	X		
	9													X											X	X	X	X	X	X	X	X		
	10													X							3				X	X	X	X	X	X	X	X		
	11													X											X	X	X	X	X	X	X	X		
	12													X							3				X	X	X	X	X	X	X	X		
	13													X											X	X	X	X	X	X	X	X		
	14													X							3				X	X	X	X	X	X	X	X		
	15													X											X	X	X	X	X	X	X	X		
	16				X									X											X	X	X	X	X	X	X	X		
	17													X							3				X	X	X	X	X	X	X	X		
	18													X											X	X	X	X	X	X	X	X		
	19													X											X	X	X	X	X	X	X	X		
	20													X											X	X	X	X	X	X	X	X		
	21													X											X	X	X	X	X	X	X	X		
	22													X											X	X	X	X	X	X	X	X		
	23													X											X	X	X	X	X	X	X	X		
	24													X											X	X	X	X	X	X	X	X		
	25													X											X	X	X	X	X	X	X	X		
	26													X											X	X	X	X	X	X	X	X		
	27													X											X	X	X	X	X	X	X	X		
	28													X											X	X	X	X	X	X	X	X		
	29													X											X	X	X	X	X	X	X	X		
	30													X											X	X	X	X	X	X	X	X		
FEB	1													X											X	X	X	X	X	X	X	X		
	2													X											X	X	X	X	X	X	X	X		
	3													X											X	X	X	X	X	X	X	X		

Fig. 71.—Record sheet marked by the nurse every day. It presents graphically the patient's waking behavior and the amount of sleep. The headings under behavior are arranged so that manic ones are to the reader's left, normal in the middle and depressed to the right. A glance shows that this patient's reaction was mixed.

- daughter stay with the patient as much as possible. (4) Keep the door open and the window closed when no one is with the patient. (5) Add occupational therapy to her routine.

This went fairly well for a week but on December 12th she was still asking for her daughter and saying her son had been killed. She was transferred to the psychiatric ward and the next day she was still noisy. She had a firmly fixed belief that her family was dead; she prayed and called to them in Portuguese. Her behavior improved a little in the next four weeks. After January 5th, except for being resistive to manipulation and feeding, she was not a behavior problem in the daytime. She became less agitated and less noisy, but remained irritable and resistive. There was marked improvement by January 16th (Fig. 71) and on January 23rd she was allowed up in a wheel chair. Her mood improved and she was cooperative and at times smiled pleasantly. Her nights did not become quiet until January 18th (Fig. 71). As indicated in the left hand column of the sleep graph the patient had paraldehyde on an average of 3 drachms every other night for the first month. After January 18th, she slept well without medicine. By February 2nd she was practically normal and was returned to the orthopedic service, whence she was discharged to her home. March 1st she reported to the outpatient department and was well except for a slight feeling of depression at times.

DISCUSSION

The important fact brought out by these cases is that they get well if given individual attention with proper psychiatric nursing care. A light should be left in the room as long as hallucinations persist, and dark shadows and hangings must be avoided. It is important to let them have visitors who can reassure them. The relatives and the priest are invaluable but must be coached by the physician. A few words in their own language often seem to quiet them remarkably.

It is usually necessary to reduce the use of sedatives drastically. As indicated in the case abstracts most of these psychotic disturbances came on a few days after an operation when morphine or other drugs had been given routinely. The point is not that too much drug was given, but that these patients seem to be particularly affected by drugs, and improve when the medication is omitted. Paraldehyde is the sedative we use most; from 2 to 3 drachms by mouth or 4 or 5 by rectum will give most patients a fairly good night's rest and

will not leave them confused and depressed the following morning.

It is of especial interest that all of these patients are foreigners, and most of them have language difficulty. They feel truly outlandish (in the real sense of the word) and they act that way. The environment is new and strange, the customs of the hospital are nothing like those in their homes. Even the speech is difficult to understand. Many of them were brought to the hospital after an entirely inadequate explanation. Once on the ward, the busy staff looked after them well, but the doctors did not make an effort to find out if the patient really knew before operation what it was all about, just what the procedure would be and why it was necessary. Then came the operation; normal fears were exaggerated by loneliness and strangeness. After operation when drugs cause dreaminess and confusion, these people get panic feelings, ideas of persecution and punishment and even delusions and hallucinations. The duration of the psychosis is from one to several weeks and the delusions, hallucinations and ideas of persecution that at first look schizophrenic seem to clear up fairly quickly, go over into a diffuse anxiety state with depression and then disappear entirely.

It is suggested that careful psychologic preparation for the operation by means of interpreter or better a priest who speaks the patient's language, would make postoperative psychoses less likely to occur. In addition drugs should be used sparingly. If psychosis occurs, the patient should be moved to a single room and special psychiatric nurses who can speak her language should take care of her. Visitors of her own nationality should be admitted. Hydrotherapy with occasional doses of paraldehyde should be enough to quiet the patient. Morphine must be avoided unless pain is intense, because the confusion it causes is usually more disagreeable than the pain. As the patient improves, she should be encouraged to talk, interpersonal relations should be cultivated and she should be kept busy by the occupational therapist.

The differential diagnosis between this type of psychosis and the usual postoperative delirium rests largely on the fact that these patients are well oriented: they know who they are, they recognize the doctor, they know the name of the hospital

and the approximate date. They misinterpret for a time, and make a nurse into an angel or a doctor into a friend, but there is nothing like the complete disorientation and confusion of the toxic delirious reactions. Moreover, there is little fever or cause for considering toxic factors as of great etiologic importance. Drugs were not used in excess in these cases, rather, it seems, a moderate dosage of drugs caused excessive misinterpretation of the environment because the patient had reason to be confused and afraid before the operation. The mood is one of fear. This with confusion makes a state of mind where paranoid ideas easily develop.

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THE DIAGNOSIS AND TREATMENT OF VASCULAR LESIONS IN THE BRAIN

DISTURBANCE of the circulation is by far the most common cause of lesions in the brain. The diagnosis and treatment of such cases is by no means confined to the specialist, for they are problems that arise frequently in the daily practice of all physicians. It is important, therefore, that the general practitioner should be able to differentiate between the different varieties of cerebral vascular accident and other lesions of the brain. An intimate knowledge of the detailed anatomy of the nervous system is not necessary, nor are any special instruments required. The differentiation between the various types of cerebral vascular accident and between them and other cerebral lesions is important not only from a prognostic viewpoint, but also in regard to treatment. For example, the prognosis and treatment of primary subarachnoid hemorrhage is quite different from that of an intracerebral hemorrhage. The failure to make the correct diagnosis in a patient with a subdural hematoma will result in an unnecessary fatality. It is not sufficient in present-day practice indiscriminately to label all patients with cerebral symptoms of acute or subacute evolution as "cerebral hemorrhages." The purpose of this article, therefore, is to present a few facts which will help in the differential diagnosis of such lesions.

Cerebral vascular lesions may be divided into 4 groups, primary subarachnoid hemorrhage, cerebral embolus, cerebral hemorrhage, and cerebral thrombosis. The chief conditions which may be confused with vascular lesions are brain tumor, brain abscess, traumatic subdural or extradural hemorrhage, epilepsy and coma due to diabetes, uremia or poisoning.

Since coma is a very frequent symptom in patients with cerebral vascular accidents, the examiner should keep in mind the proper procedure for the examination of such patients to determine whether a hemiplegia is present or not. Examination of the face and scalp for injuries, study of the fundus oculi and testing of the neck for rigidity should never be omitted. The presence or absence of a hemiplegia can be determined by observing the patient to see if spontaneous movements of the extremities are made. A facial weakness can be detected by observing whether the cheek on one side puffs out with the expiratory phase of respiration. A paralysis of the upper extremity can be demonstrated by failure of the patient to move it when it is pinched, or by lifting both arms and comparing the way they fall to the bed. If the coma is not too deep, the hemiplegic limb will fall heavily to the bed while the unparalyzed limb will drop gradually. Paralysis of the lower extremity can be determined by lifting and dropping the legs in a similar manner, or by stimulating the sole of the feet briskly with a blunt instrument such as a key. On such stimulation the normal leg will be withdrawn, but the hemiplegic leg will remain in its original position.

PRIMARY SUBARACHNOID HEMORRHAGE

Symptomatology.—Primary subarachnoid hemorrhage is the syndrome produced by extravasation of blood into the subarachnoid space by the spontaneous rupture of a meningeal vessel. This rupture may occur because there is a congenital defect in the structure of the vessel or because of a previous aneurysm formation (congenital, arteriosclerotic or mycotic). Syphilis, strange as it may seem, is only very rarely the cause of an aneurysm of the meningeal vessels. As suggested by the variety of the causes above mentioned a hemorrhage may occur at any age, but it is most frequent in young and middle-aged adults, and may or may not be accompanied by hypertension and signs of arteriosclerosis.

Individual cases rarely vary from the classical syndrome,^{1, 2} which is so characteristic that the diagnosis can practically always be made from the history. The onset is sudden, frequently accompanying some muscular exertion, with severe pains in head which steadily increase in severity. Vomiting

and a cloudy mental condition, stupor or coma may follow in a few hours or days. In contrast to an intracerebral hemorrhage, coma or convulsions at the onset are quite rare. The salient features of the examination are a cloudy mental state, stiffness of the neck, and Kernig's sign. Hypertension may or may not be present. Significant negative findings are the absence of a hemiplegia, other focal signs or choked disks. Occasionally there may be a single or a few small retinal hemorrhages.

The laboratory examination will show a leukocytosis in the blood, usually between 10,000 and 20,000 per cubic millimeter. The urine may show albumin and casts if the case is complicated by cardiorenal disease. The first specimens of urine obtained after the accident may contain sugar, but the serum sugar content is normal or only slightly elevated. The laboratory finding that is characteristic of the disease and is never absent unless the puncture is made immediately (within three or four hours) after the onset is the presence of blood in the cerebrospinal fluid. The intracranial pressure is practically always moderately elevated (300-500 mm.) and sometimes to alarmingly high figures.

Differential Diagnosis.—The conditions which may be confused with primary subarachnoid hemorrhage are acute purulent meningitis, subdural hematoma, intracerebral hemorrhage and brain tumor. Primary subarachnoid hemorrhage has many superficial similarities to acute purulent meningitis (headache, vomiting, mental confusion, stiff neck, etc.), and the latter diagnosis is often considered. It is readily excluded by the history of sudden onset and by the results of the examination of the cerebrospinal fluid.³

Patients with subdural hematoma are often thought to have primary subarachnoid hemorrhage because the cerebrospinal fluid is usually bloody in both conditions. This mistake is made because of the failure to inquire for or to obtain a history of a recent head injury. For this reason a careful examination of the head for contusions or lacerations is important. x-Rays of the skull may be of value in some cases. The findings at the first and subsequent lumbar punctures are of great value in diagnosis.³ In subdural hematoma as in primary subarachnoid hemorrhage the pressure is high, but in the former, the removal of a small amount of fluid will cause a rapid fall in the pressure,

whereas in primary subarachnoid hemorrhage, it is necessary to remove large amounts of fluid to reduce the pressure.

Brain tumor or brain abscess may cause some difficulty in diagnosis, but the presence of blood in the cerebrospinal fluid excludes these diagnoses.

The differential diagnosis between primary subarachnoid hemorrhage and cerebral hemorrhage is not possible in many cases. The occurrence of convulsions or coma at the onset is in favor of an intracerebral hemorrhage. The development of focal signs, hemiplegia, aphasia, etc., indicates, with rare exceptions, that the hemorrhage is intracerebral.

Treatment.—When the diagnosis of a primary subarachnoid hemorrhage is made the patient should be kept in bed and the treatment directed toward the relief of the increased intracranial pressure and the meningeal symptoms. A certain percentage of cases would recover without any treatment, but without treatment the course of the disease is prolonged considerably, the patients are subjected to an extreme degree of unnecessary pain and suffering, and the mortality rate is much higher. Owing to the temporary nature of the pathology, primary subarachnoid hemorrhage is especially amenable to treatment by lumbar puncture. The removal of fluid by lumbar puncture reduces the intracranial pressure and relieves the headache. The removal of the blood tends to alleviate the meningeal symptoms. Sufficient fluid should be removed at first puncture to bring the intracranial pressure to the low limits of normal (80–100 mm.), and the puncture repeated at frequent intervals. The danger of lumbar puncture in these cases has been overemphasized. There is no adequate physiologic basis for the hypothesis that removal of fluid by lumbar puncture tends to increase the hemorrhage, and empirically it has been found to be untrue. The frequency of punctures should be governed by the rapidity of the return of the symptoms and the level of intracranial pressure encountered at the previous puncture. In the average case 2 or more punctures are required daily for the first two to three days, single punctures for the next three to six days, and occasional ones in the ensuing two weeks. The frequency of punctures can be governed by the level of the cerebrospinal fluid pressure about as follows:

<i>When pressure is</i>	<i>Repuncture in</i>
Over 400 mm. of cerebrospinal fluid.....	12 hours
250 to 400 mm.....	24 hours
180 to 250 mm.....	24 to 48 hours

When the pressure is below 180 mm. on 2 or more subsequent punctures several days apart, further punctures are not needed, provided most of the blood has been removed by this time. In the usual case for the first two or three days the pressure rapidly rises to or near to its original level within twelve to twenty-four hours after each puncture. This is due to the more rapid formation of cerebrospinal fluid resulting from the meningeal irritation and an impairment of the absorption of the fluid resulting from plugging of the arachnoid villi by the blood. After three to four days the pressure begins to become progressively lower on each subsequent puncture and

TABLE 1
THE CLINICAL COURSE OF TWO TYPICAL CASES OF PRIMARY SUBARACHNOID HEMORRHAGE AS ILLUSTRATED BY THE CHANGES IN THE CEREBROSPINAL FLUID

Cerebrospinal Fluid								
Case.	Date.	Pressure mm.	Character of fluid.	Cells per cmm. R B.C. W.B.C.		Protein mg. per 100 cc.	Sugar mg. per 100 cc.	Colloidal gold.
1	Jan. 20	400	Bloody xanthochromic.	98,000	1700	...	8	
	Jan. 21	480	Bloody xanthochromic.	98,000	1700	138	38	
	Jan. 21	450	Bloody xanthochromic.	14,800	1200	38	..	
	Jan. 22	450	Bloody xanthochromic.	5150	316	45	70	
	Jan. 23	330	Xanthochromic	62	9	44	65	
	Jan. 24	230	Xanthochromic	125	44	60	62	
	Jan. 28	200	Xanthochromic.	106	12	41	37	
	Feb. 3	170	Colorless.	0	28	31	61	
2	May 6	300	Bloody xanthochromic.	250,000	750	...	91	
	May 7	220	Bloody xanthochromic.	35,200	...	154		
	May 8	260	Bloody xanthochromic.	3750	70	122	91	0000000000
	May 12	200	Xanthochromic.	54	2	61	...	0011100000
	May 16	210	Slightly yellow.	61	6	31	...	1111000000
	May 22	180	Colorless.	7	12	33	...	0000000000

Case 1. Thirty-two-year-old Italian male, sudden onset of headache on January 15th, followed by vomiting and stiff neck. In bed at home until January 26th. Semistuporous, temperature 101° F., blood pressure 150/95, stiff neck and Kernig's sign. No focal signs or choked disks. Discharged well after two weeks.

Case 2. Thirty-eight-year-old Swedish female. Sudden onset of headache on April 30th. In bed at home until May 6th, with severe headache and vomiting. Drowsy, stiff neck, Kernig's sign. Temperature 101° F., blood pressure 150/90. No focal signs or choked disks. Discharged well after fourteen days.

is usually normal after ten to twelve days. The fluid which is frankly bloody on the first few punctures gradually becomes less bloody and more xanthochromic for five to eight days, then the xanthochromia begins to disappear, and the fluid is entirely normal by the fifteenth to twentieth day. Two cases illustrating the evolution of the changes in the cerebrospinal fluid are given in Table 1.

CEREBRAL EMBOLUS

Symptomatology.—Cerebral embolus is usually the result of a release of a thrombus from diseased heart valves or muscle (bacterial endocarditis, auricular fibrillation or cardiac infarction). Owing to the nature of the underlying pathology, cerebral embolus may occur at any age. Prodromal symptoms, headaches, and vomiting are quite frequent. The onset is usually sudden accompanied by headaches in about 25 per cent, coma in 25 per cent and convulsions in 10 per cent. Focal signs are practically always present, and since multiple emboli are the rule, bizarre clinical pictures often result. Laboratory data of importance are a leukocytosis in the blood, positive blood culture in cases of bacterial endocarditis, and the findings in the cerebrospinal fluid. The cerebrospinal fluid pressure is usually normal, but occasionally it is slightly elevated. The fluid is usually clear and colorless. If the embolus is septic, there may be a mild or moderate pleocytosis in the fluid and occasionally the fluid may be bloody from the rupture of a mycotic cerebral aneurysm.

The prognosis in patients with cerebral emboli is usually poor due to the nature of the process causing the embolus. Cerebral emboli are quite common in bacterial endocarditis, which is almost invariably a fatal disease. Embolism may occur in patients with auricular fibrillation. In such cases blood clots may form on the walls of the auricle and a fragment from such a clot lodge in a cerebral vessel. The prognosis in such cases depends on whether a large or a small vessel is occluded by the clot and whether there are one or more emboli. Occlusion of the common carotid, internal carotid or the main trunk of the middle cerebral artery is usually fatal in elderly individuals. A third cause of cerebral embolism is the breaking off of a small clot of blood which has formed on

heart muscle undergoing necrosis following coronary thrombosis.

Differential Diagnosis.—The signs and symptoms of a single cerebral embolus are usually quite similar to those of cerebral thrombosis. The differential diagnosis depends on the results of the examination of the heart. When the emboli are multiple, bizarre clinical pictures⁴ may result, suggesting diagnosis of an encephalitis, brain tumor, brain abscess or syphilis of the nervous system. The important points in the differential diagnosis favoring cerebral embolism are: (1) a septic type of temperature, (2) an abnormal heart, (3) normal or only slightly elevated intracranial pressure, (4) negative serum and cerebrospinal fluid Wassermann reactions and (5) a positive blood culture.

Treatment.—Treatment of the neurologic defects in the patients that recover from the initial insult is the same as that in cerebral thrombosis or hemorrhage.

CEREBRAL THROMBOSIS AND HEMORRHAGE

Symptomatology.—These two conditions are considered together because they have many clinical similarities. They are both usually a complication of cerebral arteriosclerosis, but either may occur in young patients with apparently normal cardiovascular systems. Cerebral thrombosis may occur in infants and children as a complication of acute infections, and in young or middle-aged adults with normal blood pressure as a result of syphilitic arteritis.

The differential diagnosis between cerebral thrombosis and cerebral hemorrhage in a given case is extremely difficult. There is not one clinical sign that will differentiate the two conditions with absolute accuracy. The presence of blood in the cerebrospinal fluid is diagnostic of a hemorrhage, but since cerebral hemorrhages rupture into the ventriculosubarachnoid space in only 75 per cent of the fatal cases, and probably in a much smaller percentage of the nonfatal cases, a clear cerebrospinal fluid does not exclude the diagnosis of cerebral hemorrhage. The following points are of value in the differential diagnosis between cerebral hemorrhage and thrombosis, and when one or more are present the diagnosis of cerebral hemorrhage is indicated⁵:

1. Onset with headache and vomiting or convulsions.
2. Stiffness of the neck or Kernig's sign.
3. Dilatation of pupil on paralyzed side.
4. Conjugate deviation of the head and eyes.
5. Bilateral Babinski reflex.
6. Progression of the focal neurologic symptoms.
7. Leukocytosis over 12,000 per cubic millimeter.
8. A cerebrospinal fluid pressure greater than 350 or 400 mm.
9. A bloody cerebrospinal fluid.

The mortality rate of cerebral thrombosis is very much lower than that of cerebral hemorrhage. A cerebral hemorrhage of any appreciable size is practically always fatal.⁶ This is particularly true when the hemorrhage is large enough to break into the ventricular system. Statistics as to the incidence of the various forms of cerebral vascular lesions based on necropsy material show a higher percentage of hemorrhages than thromboses.⁵ This is due not only to the fact that the mortality rate is greater but also because, as explained below, death occurs more rapidly in the patients with hemorrhages. Death in patients with hemorrhages is usually the direct result of the hemorrhage so that attention is directed to the brain at necropsy, while in cerebral thromboses on the other hand, death is often due to pneumonia, uremia or cardiac failure and examination of the brain is omitted at necropsy. Analysis of clinical material shows, as would be expected, a much larger incidence rate of cerebral thrombosis than of cerebral hemorrhage. In an analysis of over 600 cases the incidence rate for the various cerebral vascular lesions was found to be as follows: thrombosis 66 per cent, hemorrhage 21 per cent, embolus 5 per cent, primary subarachnoid hemorrhage 8 per cent.

Cerebral vascular lesions are practically never the cause of sudden death.⁸ Death may occur, however, in only a few hours in patients with a massive cerebral hemorrhage, and about 90 per cent of the fatalities are within two weeks of the onset.⁵ A cerebral thrombosis is only rarely fatal within twenty-four hours, and usually several days or weeks elapse between the thrombosis and death.

The short branches of the middle cerebral artery are the source of the hemorrhage in nearly two thirds of the cases,

with the thalamus, internal capsule and adjacent basal ganglia suffering the greatest damage. The remaining vessels are the source of the hemorrhage in the following order of frequency, the long branches of the middle cerebral, the anterior cerebral, the posterior cerebral, and the basilar artery. Practically the same order of frequency obtains for thrombosis of these vessels.

Differential Diagnosis.—The differentiation between cerebral hemorrhage and thrombosis and other cerebral lesions depends chiefly on the history. The onset of cerebral vascular lesions is sudden. If this fact is kept in mind, many mistakes in diagnosis will be avoided. The conditions which give the most difficulty in diagnosis are: brain tumor and subdural hematoma. Other causes of coma such as uremia, diabetes mellitus, alcoholism and epilepsy can be excluded by the history and by a chemical analysis of the serum.

Cerebral hemorrhage can be differentiated from brain tumor by the finding of blood in the cerebrospinal fluid. Hemorrhages may occasionally occur in brain tumors but they rarely are of sufficient size to rupture into the ventricles. The diagnosis between cerebral thrombosis and brain tumor is more difficult. The slow or subacute evolution of signs or symptoms indicates the diagnosis of brain tumor, as do also choked disks or an intracranial pressure greater than 300 or 350 mm. An increase in the protein content of the cerebrospinal fluid to 100 mg. per 100 cc. or more is almost pathognomonic of a brain tumor.³

Subdural hematoma is distinguished from cerebral thrombosis by the history of a recent head trauma and by the subacute evolution of symptoms. The presence of arteriosclerosis and hypertension favors the diagnosis of thrombosis, but it must be remembered that a blow of insufficient intensity to produce a subdural hematoma in a normal individual may do so in an arteriosclerotic patient. It has also been shown that a subdural hematoma may cause a mild or moderate elevation of the systemic blood pressure, which falls to normal after the hematoma is removed by operation.⁹ The examination of the cerebrospinal fluid is of considerable value in differential diagnosis. In cerebral thrombosis the fluid is usually clear and under normal pressure. In subdural hematoma the pressure

is usually slightly or moderately elevated. In patients with subdural hematoma the fluid³ is usually bloody for the first week after the injury, xanthochromic for another week and then clear and colorless. The appearance of cerebral symptoms, such as headache, mental confusion and focal symptoms in a patient who is chronically or periodically addicted to the use of alcohol, should lead to the suspicion of a subdural hematoma, since such patients often suffer minor or severe head injuries which they do not remember.

Treatment.—The treatment of a patient with a cerebral hemorrhage or thrombosis in the acute stage is supportive in nature directed toward helping the patient survive the insult of the “shock.” Respiratory and cardiac stimulants (caffeine, digitalis, oxygen) should be used when indicated. The value of venesection in these cases is still disputed, and the conservative opinion is that it should only be used when there are signs of congestive heart failure. Fluids and liquid diets should be given by mouth if patient is able to swallow, but if he is too comatose to swallow, saline and glucose should be given parenterally. The bladder should be emptied by catheterization if it is distended, and the catheterization repeated as often as necessary. The bedclothes should be changed immediately when soiled by the patient, and the position of the patient in bed changed frequently to prevent the development of bed sores and pulmonary congestion. Lumbar punctures are of doubtful value in the treatment of the average case of cerebral thrombosis or hemorrhage. They are occasionally necessary to aid in the establishment of the diagnosis, and are not infrequently of value in relieving the symptoms and signs of increased intracranial pressure in hemorrhages, particularly when the increased intracranial pressure is due in part to the blood which has ruptured into the ventriculosubarachnoid space. Punctures should be repeated in the cases where a large amount of bloody fluid can be removed.

After the patient has recovered from the “shock” and the danger to life has disappeared, the main therapeutic efforts should be directed toward cure or alleviation of the neurologic symptoms and the disease process which produced the hemorrhage or thrombosis. Arteriosclerosis is the most common cause of cerebral vascular lesions and since there is no ade-

quate treatment for arteriosclerosis, the further treatment in the majority of the patients is chiefly a problem in physiotherapy and psychotherapy. If the results of the examination of the blood and cerebrospinal fluid indicate that syphilis is playing a rôle in the vascular pathology, it should be treated. A cerebral hemorrhage practically never occurs in a patient with syphilis unless there is a high degree of concomitant hypertension and arteriosclerosis. Cerebral thrombosis, on the other hand, is quite frequent in patients with syphilis, both with and without an accompanying arteriosclerosis or hypertension. For this reason the blood and spinal fluid of all young or middle-aged patients with a cerebral thrombosis should be examined serologically for syphilis, regardless of whether arterial hypertension is present or not. If the serologic test for syphilis is positive in either serum or cerebrospinal fluid, the patient should be treated for syphilis. Dramatic results cannot be expected of such treatment, however, since most of the symptoms in such cases are due to softening of brain tissue resulting from occlusion of the vessel. If there is a mild or moderate degree of syphilitic meningitis also present, some of the symptoms may be due to the inflammation which will respond to the treatment. In the usual case, however, the most that should be expected from antiluetic therapy is the possible prevention of further vascular lesions. Treatments in such cases should be potassium iodide by mouth, and a series of 1 to 15 intramuscular injections of bismuth every five to seven days, followed by 10 to 15 intravenous injections of small doses of neosalvarsan (0.3–0.6 Gm.) at weekly intervals unless contraindicated by cardiac decompensation or aortic aneurysm. Alternate series of bismuth and neosalvarsan should be given until patient has had 30 to 40 injections of each, or until the cerebrospinal fluid is normal in the patients in whom the fluid was abnormal.

In rare instances a cerebral hemorrhage may become encapsulated and present the symptom-complex of a tumor. Such hemorrhages have been removed successfully in several instances^{10 11} but this mode of therapy is still in the experimental stage and is adapted to only a very small percentage of the cases of cerebral hemorrhage.

The important part of therapy in the patients that live is

the treatment of the residual neurologic symptoms. The hopeless attitude taken by many physicians is unjustified. Much can be accomplished by physiotherapy and reeducation. As soon as the patient recovers from the shock of the accident, all of the muscles of paralyzed extremities should be massaged daily. The joints should be passively moved, encouraging the patient to try to help in the movements and gradually allowing him to do most of the work. A cock-up splint should be applied to the wrist and hand to prevent contractures of the wrist and finger muscles, and a posterior splint or shell to the leg and foot to prevent toe and foot-drop. The patient should be given a rubber ball to move around in his hand to aid in the return of strength and dexterity to the finger muscles. As soon as the patient is able he should be encouraged to walk with the aid of support on both sides. This should be followed by the use of crutches or cane. Persistent encouragement of the physician and family is of prime importance.

More difficult than the retraining of paralyzed limbs is the reeducation of patients with speech defects. The patients should be persistently stimulated to try to talk and read, starting with simple words and pictures, and gradually increasing the complexity of the symbols as function returns. Much can be accomplished by diligence and perseverance on the part of the therapist.¹²

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HYSTERIA AS A PROBLEM IN A GENERAL HOSPITAL

APPROXIMATELY one half of all patients seeking help at a general hospital have complaints and symptoms for which psychogenic factors are important determinants. At the Massachusetts General Hospital, we have the opportunity of observing such patients over a longer period of time on the ward, and of following their development in the out-patient department. A systematic knowledge of the way in which psychogenic factors operate to cause physiologic changes is not available yet, but we are collecting data which give us some understanding of the scope of such disturbances, their major manifestations and the most promising form of management.

The present clinical report will be confined to a consideration of conversion hysteria, a definition of which is given below. This means we are not dealing with reactions of the autonomic nervous system, commonly referred to as "anxiety states," nor with the more localized disturbances in autonomic function, such as asthma and colitis, which lately have been recognized as having a meaningful relationship to psychogenic factors.¹

Although hysteria was recognized as a form of disease for many centuries, the term "conversion" was coined as late as 1893 when Freud described it as a condition in which qualities of excitation, attached to certain unbearable ideas, are being transmuted into some bodily form of expression: a mental conflict is converted into a state of physical distress or dysfunction.

¹ See differential diagnosis below.

The fact of the so-called "mental" determination of certain physical symptoms has been accepted by the medical profession, but unfortunately the assumption that hidden wishes and conflicts may be found at their basis, has tended to overshadow the fact which is just as true, that in conversion phenomena as in other signs of disease, we are dealing with physiologic alterations of function.

From psychologic investigations some understanding has been gained of the type of motivation and conflicts which underlie conversion symptoms. The study of physiology of these persons is still very much in its infancy. It is due to this difference in success of the two lines of study that the habit is still current in many clinics of using the dichotomy, "organic or functional," as a seemingly valid distinction of physiologic processes. "Organic" is intended to mean "a real" lesion; "functional" is proposed to mean "just mental," imagination. As Cobb¹ pointed out, this dichotomy not only is a gross distortion of facts, but leads to a distinct disadvantage for the patient whose condition has once been labelled "functional." One is inclined to give up further physiologic investigations after one once feels that one is dealing with a psychoneurosis.

All diseases are disturbances of function. In some, morphologic changes are important factors; in some the lesions are not visible; while in others the pathology is of a reversible kind. We have to weigh in each case the relative significance of morphologic, serologic, chemical and psychologic factors.

Definition.—A person suffering from hysteria presents dysfunction or distress which is related to his management of his social environment. There is an amnesia for the establishment of this relationship between symptoms and social adjustment so the patient remains unaware of it. In addition to his symptoms, he shows characteristics of "hysterical personality make-up," which are often referred to as psychic infantilism, *i. e.*, immaturity in sexual development.

This definition implies that to establish a diagnosis of hysteria, it is not enough to merely exclude "organic disease." There must be present the positive hysterical symptoms presented in a characteristic manner, and the special type of

¹ Cobb, S.: A Preface to Nervous Disease, Chapter V, William Wood and Co., Baltimore, 1936.

personality. Moreover, the presence of a psychologic conversion mechanism does not exclude the existence of "organic disease," so one must not cease to search for lesions. The abnormalities of function are usually obvious enough.

The following two reports will serve as a starting point for a more concrete discussion of clinical problems of hysteria.

Case I.—E. B., a fifteen-year-old girl, admitted to the Massachusetts General Hospital on the Neurological Service on March 17, 1936. Her chief complaint was paralysis of right arm and leg.

Six weeks before entrance she noticed that her right arm and leg seemed to be asleep, had a feeling of "pins and needles." One day in school, while writing, her pencil fell from her hand and her right arm began to tremble. She was sent home. While waiting for a trolley car she began to feel weak and the trembling became worse, so she took a taxi. When she tried to get out of the taxi, she found she couldn't move her right leg, but she hopped into the house on her left leg. She thinks her arm was paralyzed by the time she got into the house. There was no headache, faintness, vertigo, nausea or vomiting.

The patient had always been considered as a nervous, irritable child with temper tantrums; she had had frequent colds. Three years ago, she had "the right eye turned inward" for several months after she had been frightened by a cat. Six months ago she had complained about marked pain in her right arm and thigh. For the last three months she had appeared pale and anxious and had complained about "weakness all over." Her first menstruation had occurred six months before entrance; there had been none since.

The family history showed that the mother has a disease of the left leg, which at one time was considered as cancer; that the older sister, on the basis of an early attack of meningitis, shows a deformity and weakness of the left arm, limbs and has occasional epileptic attacks.

The general medical examination showed a girl of normal development for her age without any evidence of disease of the respiratory, vascular and gastro-intestinal systems. She had a general appearance of calmness and indifference. Neurologic

examination showed normal eye movements, but the corneal reflex was reduced on the right. Facial movements were carried out better on the left than right and the nasolabial folds were more marked on left than right. There was a suggestion of rotary nystagmus and a slight tremor of the extended tongue. Her right leg was characteristically held in 45 degree flexion by tense, almost rigid muscles and there was external rotation at the hip. There was no atrophy of the thigh or calf muscles. Attempts to extend the leg at knee or hip were resisted with complaints of pain under the knee and thigh and on the anterior surface of the thigh. Active motion was limited to a few degrees of flexion at knee and hip. Passively the leg could be flexed to 90 degrees and could be extended back to 45 degrees. The foot was held in normal degree of dorsiflexion. Attempts to move the ankle were resisted with complaints of pain in the region of the knee. The tendon reflexes were more active on the right than on the left. There was an unsustained ankle clonus on the right. There was an equivocal plantar response on the right; flexion on the left. The abdominal reflexes were less active on the right than on the left. Sensation was intact over the entire body with the exception of the right leg, where there was loss of light touch, pain and temperature perception below the level of the midthigh. This sensory loss did not correspond in level to segmental or radicular distribution. There was an irregular and patchy band of hypoaesthesia extending nearly to the groin. The only area in which a sensory response was obtained below the midthigh was the sole of the foot, stimulation of which was referred to the midthigh region. Both hands were cool and moist; the skin of both lower extremities was mottled.

Lumbar puncture showed a perfectly normal spinal fluid at a pressure of 150 mm. of water. Basal metabolic rate was -21 , and repeated one month later was -29 .

A skull x-ray showed a marked increase in the convolutional markings in both sides of the skull and there was marked thinning of the skull in the occipital region. The vascular markings extended to the frontoparietal regions and were prominent. This condition, however, was bilateral. The sella turcica was small and showed no evidence of erosion or bone destruction. There were no unusual shadows within the vault.

The appearance was that of chronic increased intracranial pressure. There were no definitely localizing signs of tumor.

It was finally decided by the neurologists that the neurologic signs and x-ray indicated no brain lesion, so the patient was transferred to the psychiatric ward on March 22nd. She still had the same difficulty with her arm and leg. She would resist any attempt at passive movements and become quite upset if these were urged upon her. When not disturbed by such advances, she seemed contented and little disturbed by her paralysis. Toward the doctors and nurses, she had a distinctly defiant, often provocative attitude. Soon she began to play mischief with the nurses and seemed deliberately to do things to make the doctors angry and cause them to reproach her. Any attempt at becoming acquainted with her interests, likes and dislikes and events of emotional importance in her previous life, were met with a cool indifference; "I have nothing to say." It was quite impossible to get from the patient any trace of information concerning her own sexual development. She denied the presence of any sexual sensations and emphatically stressed that her mother had forbidden her to talk of such things.

In the course of her stay, she had several nights in which she was seriously perturbed by the fantasy that a man might be lying under her bed trying to drive a knife through the mattress into her body. She had repeated nightmares in which she felt she was being chased by a Chinaman with a knife who was just about to pierce her when she, in her fright, would drop to the ground as though she were dead. She reported in a dramatic manner a frightening experience which happened a year ago in which she and a girl friend went walking through a dark hallway, were asked by a stranger to point out the way to a room upstairs, and then discovered that the stranger was pointing a "big gun" at them. They fled in a panic.

Therapeutic efforts were made in different directions:

(A) The symptom was made undesirable for her. She was isolated from the other patients with the proposition that she might join them when able to walk. She simply disobeyed the rules, so that she became a disciplinary problem.

(B) An attempt was made to show her that there was no real paralysis: that she could move the leg, when she was

relaxed. It turned out that one day she could move it a few more degrees than another day. The matter became an issue of battling with the physician.

(C) Numerous efforts were made to obtain a more detailed account of the patient's conflicts, but she continued to be defiant and uncommunicative.

After three months she made the proposition that she would be able to move her leg for a house officer of the neurologic service, requesting that she be treated by him. She finally walked for him without difficulty, while she still insisted that she was paralyzed, in the presence of her own doctors of the psychiatric service.

She was finally discharged in August, able to walk, but leaving us in ignorance about the motivation in the background of her condition. The patient did not return to the hospital for several months, although advised to keep in touch with the clinic.

On February 12, 1937, this girl was brought again to the emergency ward. She complained of severe pain in the abdomen and both she and her father requested a surgical operation. The father stated that he had consulted 5 doctors, 3 of whom had suggested an operation. Upon examination, no evidence was found of an inflammatory process. She was referred to the psychiatric out-patient department where the following information was gained. After her discharge the patient had been fairly well until six weeks ago, when she started vomiting almost daily, refused to eat, complained about feeling bloated up and walked around in a curious posture with her abdomen noticeably protruded. Four weeks ago, she started having attacks of unconsciousness lasting from two to five minutes in which her whole body shook vigorously. In these states she did not respond to questions and had amnesia for them afterward. She also developed marked constipation for which she was given an enema every second day.

Both she and her father expressed disappointment that we did not propose an operation, they did not want any further treatment by "just talking" and went to the Beth Israel Hospital in order to get the operation there. The patient had developed the conviction that she had a peculiar round growth in her abdomen which was causing all her trouble and had to

be cut out at any cost. After refusal at the Beth Israel Hospital the patient returned to our service.

The therapeutic attack was then directed against the father, who showed extreme solicitude about the girl, and who had reported that he was supervising the enemas given to the patient. With reluctance he finally consented to have the patient placed in another home. Within three days after being moved to the foster home, all of the patient's symptoms disappeared. She has remained symptom-free with the exception of one attack of unconsciousness which occurred when she had visited her father and was taken back by him in the automobile.

In subsequent interviews in the out-patient department, the following data were elicited: the father is a disappointed man who expected to be a great musician, but is a chair-maker now. Both mother and the older sickly sister play a servant rôle in the home. The patient, a very beautiful girl from childhood, has been a favorite with her father. About ten months before the onset of her illness, the episode of being attacked by a man with a gun occurred; four months later her first menstruation occurred; and two months later one of her chums became pregnant, causing a great deal of scandal in the vicinity. Since then, the father had carefully supervised the patient's movements, warning her what might happen to her, restricting her conduct with other girls and boys. The patient developed an inclination to daydreaming, had the recurrent dream of being chased by a man with a knife, and felt frightened in her dark bedroom before going to sleep. How much sexual fantasy played a rôle in the mind of this patient we cannot say because in all our subsequent interviews the patient refused to talk about it, professing complete ignorance in such matters. She was seen once a week to give her an opportunity to discuss her life, but no significant facts have come out. Nevertheless, she has been getting along very well. The provocative and annoyed manner she showed at the time of active symptoms has been replaced by an affectionate attitude and a friendly relationship with her physician. We appreciate that under the influence of a specific situation which probably has to do with her emotional bondage to her father, her symptoms would be apt to return.

Case II.—A seventeen-year-old high school student was admitted to the Massachusetts General Hospital on the neurologic service on August 13, 1937. Four months before entry she developed a frontal headache. It persisted throughout one day and in the evening she suddenly lapsed into unconsciousness during which, she was told, her arms convulsed. The unconsciousness cleared in a half hour, and she was very weak and tired afterward. For the following fifteen days, the severe frontal headache persisted and she had approximately 15 spells of unconsciousness during that time. The headaches and spells of unconsciousness have continued. During the past month she has been unconscious seven or eight times. The patient states the loss of consciousness is always preceded by a severe frontal headache but not all of her headaches are followed by unconsciousness. She can usually foretell the latter by a sense of "tiredness" in her head, and a feeling of not wanting to "be bothered to talk to people." Recently her attacks have been preceded by laughing or crying spells. Her friends tell her that following loss of consciousness, both of her arms convulse equally. There has been no similar movement of the legs, no frothing at the mouth, and no rolling of the eyes. Her "spells" last twenty minutes to one-half hour and have altered only in the increasing frequency of their occurrence.

The parents are living, 3 sisters died of tuberculosis. Former illnesses: her sister stated that she had meningitis with "blood on the brain" at nine months. The patient has had no signs of tuberculosis. During the last few years, she has had occasional heart palpitation. Catamenia began at fourteen years of age and there has been some dysmenorrhea.

The physical examination showed no disease of the major organ systems. Blood pressure was 130/70. The patient blushed easily. There were no other signs of autonomic instability. Neurologic findings: normal cranial nerves; left leg definitely weak as compared to the right, involving all muscle groups, including those of the feet; vibration and position sense seem somewhat impaired in left leg and left arm; two point discrimination questionably impaired in left foot; no apparent impairment of touch or pain sensation. In Romberg position there is some unsteadiness and tendency to fall toward the left.

The ankle jerks are more active on the right than on the left. Plantar response is flexion on right and equivocal on left.

One of the patient's attacks was observed and described as follows: tonight at nine forty-five the patient had one of her spells. It was described that just previous to retiring she became extremely drowsy. Then after being in bed (in a four bed ward) for a few minutes, she began to cry, talking to herself, and beating with her arms across her chest. There were no clonic movements, no incontinence, tongue biting or foaming. The eyes seemed to be held tightly shut and she resisted them being opened and during this time she cried out, "I don't want to leave school, I want to go ahead and finish." This was repeated over and over.

x-Ray of the skull showed: convolutional markings slightly increased. Width of the sella is at the upper border of normal, and no evidence of erosion is present. Pineal is not visible. No unusual areas of calcification. No unusual blood vessel markings. Findings are those of increased intracranial pressure without localizing signs.

Lumbar puncture is entirely normal with somewhat low pressure.

Upon request for psychiatric consultation, the patient was seen four times in an effort at therapy. In the fourth interview she reported in detail factors in her life history which to her explained the attacks as due to her own emotional tension: the patient is the youngest of the family, the child of an intellectually ambitious mother who is married to an alcoholic man of low social status. Since the older siblings have not been successful intellectually, the mother places her hope on the patient. The patient had been very successful in her school ambitions until, after skipping a grade, she was unable to keep up her high standing. The patient had some feelings of guilt about this, blaming herself for having had "too good a time." At this same time about six months before the onset of her seizures she was walking alone at night when she was assaulted by a strange man. Having had a period of active sexual life before her puberty and having suppressed further sexual desires with some difficulty since the time of her first menstruation, she was alarmed about the intense response in herself. The interval between this episode and the onset of her attacks

was filled with a struggle between daydreaming of a sexual nature and intense effort at applying herself exclusively to intellectual pursuits. She dropped her friends and social activities and stayed at home practically all the time, having thus even more opportunity to daydream. Her first attack came in April after a period of extreme tension, sleeplessness and panic-like feelings in which the patient was afraid that something was "going to snap." She at that time feared that she might lose her mind.

The attacks disappeared and have not returned during the last six months. The large amount of information obtained in this case after relatively few interviews and the attendant change in symptomatology was, in my opinion, at least in part made possible by a methodical approach. This involved in the first hour 4 statements made to the patient expressly to remove the resistance to exploration, otherwise to be anticipated. These comprised: (*a*) the assurance of privacy, (*b*) emphasis on the impersonal character of any interview between physician and patient, (*c*) assurance that the physician is "morally neutral," (*d*) that the communication of the patient to the physician is essentially an effort on her own part at thinking things out more thoroughly, thus giving the patient an active rôle in the interview.

Case I can be considered as a classical example of hysteria: a girl in puberty who has shown signs of overreaction to frightening incidents in her childhood, and in whose family exists a case of paralysis due to brain disease, develops a paralysis of the right arm and leg, not corresponding to any neurologic syndrome. She shows remarkable lack of concern about her affliction, but a good deal of distress if efforts are made to deal with it by manipulation or examination. Her general attitude is that of indifference and defiance to the degree of actual provocation. She tells of having been assaulted by a man with a gun within the recent past. There are occasional periods of fearful daydreaming and incidents of dreams of nightmare character. The content of both day and night fantasies is that of being attacked with a knife. Except for these incidents, the patient is free from anxiety. She professes complete ignorance about any matters pertaining to sex. In the course of the observations, the symptoms are variable and seem to change in

correspondence with the patient's personal relationship to certain physicians. There is little disturbance of the autonomic nervous system. The paralysis later is replaced by other symptoms affecting a variety of organ systems (seizures, vomiting, constipation, and postural changes). The original *fear* of an operation is now replaced by a *demand* for an operation to remove something from the lower abdomen. The diverse aspects of this later development in symptomatology all become meaningful if considered in the light of a possible fantasy of pregnancy aroused by the occurrence of pregnancy in the patient's best friend. In fact this brief paragraph brings in all the important features of the clinical picture of true hysteria.

The second patient is a young girl in puberty who presents attacks of unconsciousness preceded by anxiety, headache, and a vague state of intense distress. There are disturbances of motor and sensory function but no consistent evidence of a neurologic lesion. The patient's attitude is that of lacking concern about her attacks and of challenge to her physicians. She has wondered whether she might need an operation. She reports about a situation of a recent assault by a man. There is no history of "nervous instability" in her earlier life; the story is rather that of an ambitious girl who has substituted intellectual endeavors for the "give and take" relationships with other young people. She has been oblivious to the presence of sexual fantasies aroused in her by the assault situation until they came to light during the psychiatric interview and were recognized by her as a source of intense conflict.

With this outline as a starting point, I will now discuss the several aspects of hysteria in its pure form:

(4) **Occurrence.**—Hysteria is predominantly a disease of young girls. In older women we would be hesitant to make the diagnosis unless able to establish a history of similar difficulties reaching back to the age of puberty. A clear-cut hysterical picture without any premonitory signs at an age beyond thirty-five is extremely rare.

The capacity for conversion is probably present in everyone as was evidenced by the great number of psychogenic symptoms during the War, but there one found very serious emotional strain (fright, trauma) and often an obvious material gain or escape from unpleasant situations. It seems important

to stress that in the common picture of hysteria as seen in practice an inner conflict closely linked up with the patient's sexual development is the important issue, while the "secondary gain" (for instance, not having to go to school, or winning attention) is of minor importance. Hysteria is much rarer in men than in women. Conversion symptoms occur also in children, but the typical period for the development of the picture of hysteria is adolescence.

(B) **Symptomatology.**—The symptoms do not correspond to any medical or neurologic syndrome; they are variable, dependent upon the method of examination and upon the person who does the examination. The attitude of the patient is that of indifference, but any attempt at disproving the somatic nature of the symptoms meets with anxiety and dramatic protest.

The typical hysterical manner of presenting symptoms is different from that seen in other neuroses. In the anxiety states, the patient reports his troubles with expressions of obvious distress. These are series of discomforts which fall in line with overreaction of the autonomic nervous system. In the hypochondriac states, the patient registers concern lest something might be wrong with parts of his body; if reassured about his symptoms he readily discards old ideas but continually brings up new evidence. This distinction is of great clinical importance because the prognosis of hypochondriac state is worse than that of hysteria and the management of anxiety state is different from that of hysteria.

The general attitude of patients with hysteria rarely misses the coloring of defiance and provocation which so often succeeds in making the physicians impatient and angry.

(C) **Differential Diagnosis.**—It is our experience that particularly three other conditions are inaccurately labelled hysteria, although they are different in their pathogenesis and require different managements.

1. States of distress due to overreaction of the autonomic nervous system. In this condition the patient complains about more or less intense distress, variable and often occurring in attacks. This distress is accompanied by positive signs of autonomic instability: tremor of extended hands, circumoral pallor, tachycardia, or blushing, marked dermatographic re-

sponse, perspiration, salivation. We refer to these conditions as *anxiety states*.

2. States of overconcern about certain organs or parts of the body without the occurrence of true conversion symptoms. The essential complaint of such patients is the conviction that something "must be wrong" but they have great difficulty in describing their evidence of disease in anything but vague terms, and they do not show any active changes of function. This condition is referred to as *hypochondriasis*.

3. Finally, one should differentiate between true hysteria and conditions in which disturbances due to original anatomic lesions (for instance, head injury) do persist because of what is sometimes called "psychic superstructure." These patients in whom immediate material gain, such as financial compensation, lends a certain value to their symptoms, would better be dealt with in a separate discussion. The main symptom-sustaining element in such conditions is "the secondary gain." They require a special form of treatment.

(D) **Morphology.**—It is logically axiomatic that there can be no change in function without change in structure. Today, however, we have few methods for observing these subtle and often reversible structural changes, so we must rely on observing coarse lesions with the eye and somewhat finer ones with the microscope. In the 2 patients described there were various abnormalities in the function of the neuromuscular system, but an autopsy on either of them would probably have shown nothing. The x-ray of the skull in each case showed a thin cranium with "mottling" indicative of increased intracranial pressure, but the lumbar puncture proved that there was no such increase. It must be remembered that skulls of children often appear thin and that it is not uncommon to find physical as well as psychic infantilism in patients with hysteria.

(E) **Physiology.**—Although there were no recognizable lesions in our patients, there were marked disturbances in the physiology of the nerves, muscles and viscera. In certain patients the symptom-complex seems to be the somatic expression of fantasies. The first patient acts as though she was pregnant and expected to have an operation for delivery. Her interest in these matters has been mightily aroused by the pregnancy of her friend. She acts as though she was preoccupied

with the problem of delivery: her vomiting, her fecal retention, her demand for an operation, and her posture with protruding abdomen, all fit into this picture. Yet, there is nothing in the patient's thoughts which corresponds with the assumption of such a fantasy. The conclusion seems incapable, that a situation which has the power of inducing certain responses of thought and imagery, may find its expression in a series of somatic responses, the relationship between fantasy and symptom being masked by amnesia. In addition to the physiologic changes directly related to responses of this sort, one often meets physiologic variations which are secondary to the main symptoms, *i. e.*, to the way in which the patient acts out his response. Examples are: atrophy of disuse, hypertrophy from excessive use of muscles as in tremors and tics, alkalosis and tetany brought about by panting and hyperventilation.

(F) **Psychology.**—The patients are in a serious conflict situation. The defiant and provocative demeanor is part of the disease and disappears with the symptoms. The presence of overwhelming fears, particularly of dark places and the anticipation of assault or injury play an important part in the patient's life. The night dreams are characteristic. They are usually scenes of threatening injury from which the patient tries to escape. The transformation of the original fear of injury into a later demand for injury in the form of an operation is a very characteristic process in hysteria, and is responsible for the fact that so many of these patients who finally reach a psychiatrist, have undergone a number of exploratory operations because the demand becomes so violent and their symptom presentations so dramatic that it often is difficult for the physicians to refuse exploratory operation. It is in these instances that a psychiatric investigation can be of greatest assistance in establishing the nature of the patient's condition.

(G) **Prognosis.**—Many conversion symptoms disappear in a surprising manner as soon as the causal situations disappear, but the inclination toward new symptom formation is deeply linked up with the fantasy life of the patient and can be dissolved only by a thorough investigation. The physician must study the conflict trends in the patient and their emo-

tional reactions, which are strongly conditioned by earlier disturbing experiences.

Surgical operations, particularly pelvic, reduce the hope of successful treatment. Such procedures confirm her own belief that her distress is due to "organic disease," *i. e.*, something beyond her control, giving her the alibi she longs for.

(H) Management.—A variety of methods is available for the treatment of hysteria: (1) A thorough rearrangement of the patient's inner fantasy life and her adjustment so far as her sexual development goes, can be brought forth most efficiently by psychoanalytic procedure. This procedure at present is not feasible in many cases because of its length and costliness. (2) It may be possible to gain a fair amount of information about the factors in the patient's environment which set up the stimulus to which the patient's symptoms are the response. In our first patient, the separation of the patient from her father was immediately followed by a much more definite change than any former attempt at exploration. In the second a brief study brought the traumatic situation to light. (3) A patient may be forced to abandon a particular symptom by direct suggestion in the form of hypnosis. In this case, we remain ignorant about the factors determining the abnormal response and we do not remove the propensity to further symptom formation. Hypnosis may be replaced by other methods of more indirect suggestion, such as the use of electricity or certain kinds of medication, but these usually have only a temporary effect which is largely dependent upon the authority which the physician is able to exert over the patient—these may be described as the explorative, the environmental and the suggestive methods and the choice of procedure in a given case will depend upon the specific situation of the patient.



CLINIC OF DR. EDWIN M. COLE

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DISABILITIES IN SPEAKING AND READING

IN a clinic devoted to the problem of disordered function in language a large amount of apparently quite diverse material is met with. The cases are such as are seen by physicians the country over and it may be of interest to consider them here.

The realization of certain facts is important to the worker in a language clinic. What are these facts? The first and most obvious is the value amounting to necessity for the individual nowadays to master language. The second is that language is nothing more nor less than a quantity of symbols, symbols of actions, motions and their results such as feelings. Thus language is a system of symbolic representation. As such, like any code, it must be learned in order to be of use. But it is precisely here that many patients have difficulty. There are great variations between individuals in their ability to learn the code. We are all more or less aware of this. We know that some people talk with ease, others not. Some are rapid, accurate readers, others read laboriously. Some spell well, others with many errors. Some write clearly, others illegibly. Similarly we observe that there are people who can with ease develop great skill and proficiency in music and other arts; in tennis or other athletics, and in the whole gamut of skilled acts that mankind has attempted. Differences in performance are due to diverse individual endowments. Some people are sufficiently gifted in a given line to be successful in that line without apparent effort. Others, without particular talent, still may achieve satisfactory results through deliberate acquisition of the requisite skills. A third group is unable to master the necessary technics, or skills, owing to a complete lack of talent.

It would seem, then, that many of our achievements are the result of our heredity—as shown by our innate gifts and deficiencies. We are interested here in deficient performance in language. Let us review some of the material seen in a clinic devoted to language problems, for such material, diverse as it is, may have a common denominator which, if appreciated, will throw light upon the handling of such cases.

I need hardly say, that I am not considering language deficiencies due to blindness, deafness, a congenital defect, or disease affecting the speech apparatus, foreign schooling, parentage, or other similar causes of inadequate exposure to the language of the particular group. We are considering a physiologic dysfunction rather than anatomic variations which are self-explanatory.

We see three types of speech case frequently. The first of these, is motor speech delay. This is a particularly trying condition as far as the patient's family is concerned. Parents see a child develop normally. He may feed well, he may be trained readily, he may sit up, stand and walk as expected, he seems to hear and understand but he doesn't talk! What is mild disappointment on the part of parents when a child of eighteen months doesn't talk, becomes annoyance at the silence of two years, apprehension at the silence of three years, and great concern at the silence of four years. This concern is intensified by tales brought by well meaning neighbors or friends who knew of somebody who couldn't talk because he had a shock or brain tumor, or again somebody's child who was mentally retarded and hence unable to speak. These differential diagnoses pass through one's mind but usually they can be ruled out easily. The child in question is neurologically sound. He seems bright and attentive to what goes on about him. He obeys directions well. Yet, his speech is either entirely absent or consists of a confused jumble of sound which we do not recognize as our language.

A second type of speech disorder, is a speech replete with infantilisms. This we know as "baby talk." It exists to a varying degree, often being so slight a deviation from normal speech that nothing is done about it. The following case will serve as an illustration.

Case I.—A boy of four years, three months, was brought in because his speech was so indistinct that he could not be understood by the children in the kindergarten which he attended. In spite of this, he had seemed to be a bright and intelligent child both at home and at school. His birth and early development were uneventful. He had had no serious illnesses. He walked at nineteen months but did not begin to talk until three years, and then only a few indistinct words. Thereafter he learned to talk more fluently, but always in a modified language of his own which was largely ununderstandable to strangers. He had always shown a marked preference for the use of his left hand, and no attempt had been made to interfere with this.

The family history is interesting. The paternal grandfather is left-handed. A brother aged seven did not talk until he was four, and now is having a great deal of trouble learning to read.

The patient presented a very infantile speech. It was striking that there were no speech sounds which he could not imitate. He was an intelligent youngster, showing no abnormalities other than in his speech.

In more severe cases the child's speech is so far from normal that only the mother can understand it, and she must act as an interpreter. At this point it should be said that a great many factors enter into baby talk, once established, which tend to perpetuate it. Baby talk may be thought "cute," and thus rewarded, becomes a source of satisfaction to the child. Or, a tolerant mother allows herself to be a willing slave to the youngster whose speech she must interpret. The child in this situation is overprotected and will with difficulty give up the speech which ensures for him a favored position. Again a child may cling to infantile speech in an attempt to compete with a younger sibling who has displaced him in the comfortable position of baby in the family. There are, of course, many other variations on this theme, which must be taken into account when working with the child and his family. However, in my experience the most important factor in the therapy of both these cases is repeated, routine drills by a skilled teacher who can help the child to develop speech through a kinesthetic as well as auditory approach.

A third type of speech disturbance is stuttering. A great many of these cases present themselves in a language clinic.

Case II.—A boy of eight years was brought in because of stuttering, which had been persistent for about six years. Aside from this, there was nothing unusual in his history. His mother had noticed that his speech was at its best when he was rested and at his ease. Sometimes the stuttering seemed to be disappearing only to recur again. Of late it had been associated with blinking of the eyes.

The family history is interesting. The maternal grandfather stuttered as a boy and he was right-handed. The patient's mother knew of no left-handedness in her family, and no other instances of speech disturbance. The paternal grandfather was left-handed and stuttered. A paternal aunt is left-handed, has no speech disturbance. The father is right-handed, and stuttered from early childhood though it is now hardly noticeable. The patient is left-handed, and no attempt has been made to influence his choice of hand. Eyedness tests revealed him to be left-eyed also.

The problem that speech becomes for the stutterer, and all the personal implications involved, has been described fully in the mass of literature that has been written on the subject. We shall not attempt to add to it here. It should be said, however, that some workers have stressed the differences between cases. This has not seemed to add to the understanding of the problem. It is true that some people stutter on one group of sounds, others on another, some in one situation, others in another, some with a prolonged repetition of an initial sound, others with a complete block—or silence—at a word. We suppose there are as many individual variations as there are individuals who stutter. Similarly we hear of a great variety of cures of stuttering, each one depending on the particular point of view of the therapist involved. Each is helpful in some cases, none always so. There are, however, observations which we make with surprising regularity in our cases of stuttering. We find in our clinic as elsewhere, that the great majority of cases are males. Secondly, there is a familial feature in the 3 types of speech disturbance already described. Not only do stutterers often show a quite marked amount of

speech delay and infantilisms in their speech development, but their siblings, parents, and other relatives provide instances of the same thing. And finally, more common still, is the association of left-handedness and stuttering in the family history. It is not meant by this that the stutterer is always left-handed, ambidextrous, or one converted to the use of his right hand though indeed such cases are not uncommon. Of course, very many stutterers are purely right-handed, but, where an adequate family history can be obtained, we always find left-handed ancestors. This, in our experience, is true in the cases of motor speech delay which we have seen, and certainly in a large number of cases of baby talk. We repeat, then, that in addition to the fact that these cases have the feature of disordered speech production in common, they also share certain familiar characteristics. The obvious question—what possible connection can there be between handedness and speech, we shall attempt to answer in another part of this paper.

Problems in language development frequently come to one's attention in relation to school work. The parent of the child with a marked motor speech delay or an extremely infantile speech is forced to do something about it when the time for starting school approaches. So, too, stuttering is most often first noticed at the time when the child learns to read and write. But there is another type of language disability which in its development, presents itself solely in the school situation. Parents bring such children to our hospital clinic as they must in other places to their own family physicians, "because the teacher says he can't learn to read."

Case III.—A boy of eleven years, six months, was brought in because he could not learn to read or spell at school. He was the son of a physician and his general health had always been good. Eyesight and hearing were adequate. He had an unusually high intelligence score by a variety of psychometric tests. He had been in both public and private schools, and had had much individual tutoring, yet he had made very little progress in reading.

His family history is interesting. The paternal grandfather and greatgrandfather were left-handed. A paternal aunt is left-handed, as is the patient's father. One of the patient's

3 siblings is left-handed. The patient himself is right-handed. The father says that he himself has always had a tendency to reverse the order of letters and numbers.

As we review these cases, the situation shapes itself somewhat as follows:

At first at school, the child learns something about routines, and discipline, all of which are required for group work and for the development of skills. He then learns something of reading, writing, spelling and arithmetic—some children more rapidly than others for there is a wide range of abilities among so-called “normal” children. In a year or two, there are some who begin to lag behind others. This may be for a variety of reasons; poor physical equipment, such as poor eyesight, poor hearing, or illnesses necessitating irregular attendance. All these possibilities must be investigated thoroughly. Poor mental equipment also is a cause of inadequate performance. Here, however, I feel that we must be very careful. There is a tendency among teachers to feel that because a child doesn’t keep up with the average in being able to absorb what is taught, he is stupid, has a low intelligence. Where the intelligence is the cause of school retardation, this fact should be accurately determined and not left to the haphazard guesses of teachers and parents. The children who interest us here particularly, however, are those with good physical mental equipment but who nevertheless do not progress in school. Such children deserve careful individual investigation. If this is done, we find a group of children who have certain things in common. These have been admirably described by Dr. Samuel T. Orton, who pointed out some striking features of this group which he called specific reading disability cases, or congenital nonreaders.

After several years of school experience, a child may do uniformly well or poorly. If, however, a child makes absolutely no progress in one part of the school curriculum, though he does adequately elsewhere, and has a good intelligence, such a discrepancy is worthy of note. Children, in the third, fourth, fifth or even higher grades, who master arithmetic, have a good understanding of material used in general class discussions, adequate vocabularies, but are unable to read or spell, present such a discrepancy. Their letter patterns are

insecure and confused. The printed "b" and "d," "p" and "q," "t" and "f" and other letters are mistaken for each other. When written work is attempted, letters may appear reversed, as their own mirror images, or in reverse order as "dog" for "god." The same can be said for their reading—which is mostly guesswork. Since letter patterns are not secure words cannot be recognized. Sounds are not associated with letters. All this, in spite of the fact that arithmetic goes well, there is no demonstrable physical or mental defect, and emotionally the child seems ready to learn. The point we wish to make is the inconsistency of these cases. Bright children, able to do some of their school work, but failing where written language is concerned. At first, if no corrective measures are taken, such is the picture. Later, if the disability has not been too profound, a certain amount of reading becomes possible. This is always laborious and most inaccurate. Rarely if ever does the boy read for pleasure. His spelling remains primitive—often 4 or 5 grades behind that of the others in his class. School becomes the place in which the child has been defeated, where he has met with ridicule, as being the boy who could not learn to read and spell. His written examination papers are never completed, and are returned with caustic remarks from well meaning teachers who in this way hoped to spur the boy on to exert himself to spell and write better. Meeting with nothing but failure, the largest boy in the class, yet the slowest and poorest scholar, the only opportunity for achievement is games and pranks. In self-defense such a child is forced to become a behavior problem.

There is one feature of these reading cases which we wish to stress. That is the hereditary feature. Nonreaders are usually members of the male sex. They give a family history of left-handedness and careful questioning uncovers a brother, uncle, parent or grandparent who stutters, or who learned to talk very late, or who clung to baby talk or who never could spell and was not much of a scholar. In this, then, reading disabilities have the same familiar characteristics as other disturbances in the language function. We have found an association in families of different types of language problems, and left-handedness. It must be said, however, that left-handedness is stressed only because handedness is a fairly reliable and

quite convenient indication of which cerebral hemisphere is dominant in the language function. Thus, in most right-handed individuals the left hemisphere is dominant, while in left-handed persons the right hemisphere is correspondingly so. Speech, we all know, is regulated entirely by one hemisphere—the hemisphere dominant in the language function. Such is usually the same hemisphere which is dominant as indicated by the most skilled hand. Hence we can consider handedness as a convenient indicator of the hemisphere regulating speech. Since this is so, we can more accurately say, that we observe an association between stuttering and a heredity containing a mixture of right and left cerebral dominance.

We know, that when there is an impairment in function of certain areas of the brain, talking, the understanding of speech, reading and writing become impossible, or at least are less adequately performed, depending upon the severity of the damage. The striking fact is, that in a given individual, these areas are all in one hemisphere. Lesions in the same area of the opposite hemisphere have no influence upon the functioning of language. In this respect, language is unlike any other measurable brain function. For instance, damage to the right motor cortex or cortical fibers produces a resultant distortion of movement or paralysis, on the left side of the body while the same area involved in the left side of the brain will show similar signs of dysfunction on the right side of the body. The same can be said of sensation. However, in language, although the two halves of the brain are practically identical as to weight, cellular structure, etc., apparently only one half is important. We can say, then, that the functioning of language is entirely regulated from one side of the brain. As was intimated above, this is the so-called "dominant hemisphere." For speaking, reading, writing, and the understanding of any of these processes, we must have a perfectly functioning neurologic mechanism on one side of the brain, on the dominant side. We repeat this statement so often, because it seems to us that it is of prime importance in order to understand the factors influencing the development of language.

We can only speculate, perhaps, upon the effect of the fusion of two heredities of opposite cerebral dominance. We

are dealing with a skill—language—phylogenetically very young and consequently relatively insecure. We are dealing with a skill which to exist, depends upon the perfect functioning of a dominant hemisphere. Might it not, then, be possible, that, in fusing two inheritances which are antagonistic as far as cerebral dominance is concerned, we may impair that perfect functioning requisite for speech and reading? Much more than a speculation, is the careful and original work of Orton who first recognized the importance of cerebral dominance in developmental language disturbances.

In treating these various language disturbances we are helped by the observations we have made. To acquire facility where there is an absence of natural talent, a great deal of carefully planned, repeated drilling is essential. The drill must consistently point in one direction. It is only by repeatedly doing that for which one has little skill that one can learn to do it more easily. This does not mean that we should overlook arousing the interest and full cooperation of our patient in what we are doing. But it does mean that without exercising the defective skill we will not make it stronger.

When working with a child whose speech is either delayed or infantile one repeats simple sounds again and again until the patient can master them. Ears alone should not be relied upon. The child must be shown how the teacher uses his lips, teeth and tongue to make the sounds. In this way his sight and his kinesthetic sense will reenforce his hearing in teaching him to talk, somewhat as they take the place of hearing in teaching the deaf to talk.

Since we know that language is controlled by the dominant cerebral hemisphere and since we consider these developmental language disabilities to be the result of a poorly established cerebral dominance in respect to language we should, in our treatment, attempt to strengthen the dominance of the hemisphere. We do this by reenforcing the deficient skill through associating it with a well performed skill. For instance, we observe that many patients who stutter can read aloud with much less stuttering. Reading the words seems to reenforce their speech. We find that writing is of similar assistance. For the stutterer, then, we devise drills that associate speech with reading and writing. There are many different ways of

doing this and we must adjust the drills to the patient's performance.

In cases of reading disability these same principles are carried out. The child displays a varying degree of confusion when letters, and obviously words, are met. By associating the visual letter patterns with sound values, and with forms, as is done in seeing, sounding and writing the letter, the visual pattern finally becomes established and reading is possible. In none of these cases is anything accomplished by sporadic attempts, but only by repeated drilling can the necessary skill be acquired.

CLINIC OF DR. PHILIP SOLOMON

BOSTON CITY HOSPITAL

THE CAUSES, DIAGNOSIS, AND PROPER HANDLING OF COMA

THE patient in coma presents to the physician an emergency problem of great importance. Among the various causes of coma, there are some which require immediate treatment to save life, for example, diabetes, hyperinsulinism, poisoning, traumatic shock, exsanguination, subdural hematoma, brain tumor, meningitis, and eclampsia. Coma as a presenting sign is not so uncommon as might be supposed. At the Boston City Hospital,¹ 3 per cent of all entries are brought into the hospital in coma. The following data derived largely from the above study are presented in an attempt to aid the physician when he is confronted by a patient in coma.

Causes.—The most common causes for coma as a presenting sign and their relative frequency are: alcoholism, 59 per cent; trauma, 13 per cent; cerebral vascular lesions, 10 per cent; and the following, each forming 3 per cent or less, in order of numerical importance: epilepsy, diabetes, meningitis, pneumonia, cardiac decompensation, exsanguination, syphilis of the nervous system, uremia, and eclampsia (Table 1). It should be noted that the proportion of alcoholics entering the Boston City Hospital is undoubtedly greater than the proportion entering the average hospital because "drunks" from all parts of the city are brought here. Among the traumatic comas, injuries to the head are by far the most common cause, and it is significant that in this group subdural or extradural hemorrhages occur in 11 per cent of the cases. Among the comas due to cerebral vascular lesions, hemorrhage is more common than thrombosis (the reverse is true in cerebral vascular accidents without coma²). Barbitol or its derivatives, and carbon monoxide are by far the most common poisons which produce

TABLE 1

CAUSES OF COMA AS A PRESENTING SIGN AND THEIR MORTALITY

Disease.	Number of cases.	Per cent total comas.	Per cent non-alcoholic comas.	Cases of group ending fatally.	Per cent of group ending fatally.
Alcohol.....	690	59.1	14	2.0
Trauma.....	152	13.0	32.0	48	31.5
Cerebral vascular lesions...	118	10.1	24.7	91	77.1
Poisoning.....	33	2.8	7.0	3	9.0
Epilepsy.....	28	2.4	6.0	0	0.0
Diabetes.....	20	1.7	4.2	11	55.0
Meningitis.....	20	1.7	4.2	20	100.0
Pneumonia.....	20	1.7	4.2	18	90.0
Cardiac decompensation....	17	1.4	3.5	12	70.6
Exsanguination.....	10	0.9	2.1	10	100.0
Central nervous system syphilis.....	7	0.6	1.4	0	0
Uremia.....	7	0.6	1.4	7	100.0
Eclampsia.....	7	0.6	1.4	3	42.8
Miscellaneous.....	38	3.2	8.0	26	68.4
Total.....	1,167	100.0	100.0	263	22.5

coma. It is not generally recognized that meningitis, pneumonia, and cardiac decompensation are almost as common as diabetes and are much more common than uremia as the cause of coma as a presenting sign. Many of the patients in these groups are moribund. Miscellaneous causes of coma in the series studied were: erysipelas, burns, encephalitis, brain tumor, miliary tuberculosis, carcinomatosis, hypoglycemic shock, Stokes-Adam's disease, immersion, syncope, pernicious anemia, hysteria, ruptured ectopic pregnancy, leukemia, cholemia, strangulated hernia, septicemia and empyema.

Diagnosis.—The characteristic features of diagnostic importance in the more common causes of coma should be thor-

oughly recognized. In *alcoholic coma* one notes the alcoholic odor to the breath, the hyperemia of the face, throat, and conjunctivae, and the absence of other abnormalities. Fatal cases are likely to show in addition, cyanosis, enlarged heart, irregular heart sounds of poor quality, pulmonary râles, low blood pressure, high blood white cell count or nonprotein nitrogen.

In *traumatic coma*, the history of accident and the evidence of injury on examination make the primary diagnosis easy. To further differentiate the type and severity of the injury, and especially to recognize without delay extradural or subdural hemorrhage may be more difficult. This subject has been fully discussed by Munro.³

The most important points in the diagnosis of coma due to *cerebral vascular lesions* are the history of the sudden onset of the coma, the advanced age of the patient, the presence of hemiplegia, and an increased blood pressure or auricular fibrillation. The lumbar puncture of a bloody fluid under increased pressure is of great aid in the diagnosis of intracerebral or subarachnoid hemorrhage.

The history is the most important point in the diagnosis of coma due to nonalcoholic *poisoning*. Of importance also is the odor of the breath, the odor, appearance, and chemical analysis of the stomach washings, and in carbon monoxide poisoning, the "cherry red" color of the skin, and subnormal temperature.

The diagnosis of coma following an *epileptic convulsion* is made on entry chiefly on the basis of the history obtained from friends or relatives accompanying the patient. The occurrence of convulsions during the physical examination, and wounds or scars on the tongue are of assistance in establishing the diagnosis.

The diagnosis of *diabetic coma* is strongly suggested by the history on entry in more than half the cases in this group. Physical changes of diagnostic significance are subnormal temperature, increased pulse, Küssmaul respirations, soft eyeballs, acetone on the breath, and dehydration. Laboratory observations of diagnostic importance are glycosuria and hyperglycemia.

In the diagnosis of *meningitic coma*, the age incidence is

of importance, since half the patients in this group are children under ten years of age. Symptoms pointing to infection about the head, increased intracranial pressure, or meningeal irritation are significant in the history. Valuable diagnostic physical signs are fever, stiffness of the neck, positive Kernig's leg sign and Babinski's toe sign, and a bulging fontanel in infants. The spinal fluid will be grossly abnormal, containing increased white cells and protein, and decreased sugar and chloride. In most cases organisms can be found either by smear or culture.

Coma as a presenting sign due to *pneumonia* is more common in the young and very old. A history of previous symptoms pointing to respiratory infection is sometimes obtained, but occasionally the coma comes on abruptly without prodromal symptoms. The chief diagnostic physical signs are fever, rapid pulse and respirations, cyanosis, and signs of consolidation in the chest.

Coma due to *cardiac decompensation* occurs chiefly in individuals over sixty years of age, often with a sudden onset. A previous history of heart disease or high blood pressure is important. The chief diagnostic physical signs are cardiac abnormalities, pulmonary congestion, cyanosis, peripheral edema, and dyspnea. Other signs of venous congestion are distention of the neck veins, ascites, enlargement of the liver, and increased intracranial pressure. Abnormalities in the electrocardiograph are occasionally of assistance.

Coma due to *syphilis of the central nervous system* has a sudden onset, usually with convulsions. A history of treated syphilis is usually available. The important physical signs are neurologic: convulsions, abnormal pupils, Babinski's toe sign, and other abnormal reflexes. The blood and spinal fluid Wassermann reactions are usually positive.

In cases of *uremic coma*, a history of previous kidney trouble, high blood pressure, convulsions, or recent infections is occasionally obtained. The helpful physical signs are muscular twitchings, acetone on the breath, abnormal eyegrounds, enlarged heart, increased blood pressure, and edema of the ankles. Important laboratory changes are gross abnormalities in the urine, and increased nonprotein nitrogen of the blood.

In the patients entering the hospital in *eclamptic coma*, a history of pregnancy is always obtained. In most cases a his-

tory of convulsions and vomiting is also given. The diagnostic physical signs are abdominal tumor, rapid pulse, convulsions, peripheral edema, and increased blood pressure. The urine is always grossly abnormal.

For the purpose of differential diagnosis, the above data together with the more significant material in the diagnosis of the miscellaneous causes of coma have been grouped together in the form of tables.⁴ Table 2 lists the points in the history

TABLE 2

HELPFUL POINTS IN THE HISTORY IN THE DIAGNOSIS OF COMA AND THE CONDITIONS IN WHICH THEY OCCUR

Injury.....	trauma, hemorrhage
Previous "shocks" or "strokes".....	cerebral vascular lesions
Suicide attempt, drug ingestion.....	poisoning
Convulsions.....	epileptic coma, meningitis, cerebral hemorrhage, eclampsia, central nervous system syphilis
High blood pressure.....	cerebral vascular lesions, cardiac decompensation, uremia, eclampsia
Recent infection.....	pneumonia, meningitis, encephalitis, erysipelas, diabetes, uremia
Headache, vomiting.....	meningitis, subarachnoid hemorrhage, brain tumor
Stiffness of the neck.....	meningitis, cerebral vascular lesions
Diabetes.....	diabetic coma, hypoglycemic shock
Pregnancy.....	eclampsia, ruptured ectopic pregnancy

which are of special diagnostic value. Table 3 lists the physical changes that were outstanding in their diagnostic value. The age of the patient was of interest, since the degenerative conditions (cerebral vascular lesions, cardiac decompensation and uremia) occurred chiefly among elderly patients, while infectious conditions (meningitis and pneumonia) were more frequent in the young. Table 4 illustrates the most helpful laboratory observations.

It will be noted that little emphasis has been placed on the depth of the coma, the condition of the pupils, or the state of the reflexes. These usually are not of great practical differential value. The coma may vary in depth regardless of the cause. The pupils tend to be abnormal in the majority of cases of coma, no matter what the cause, and there is no definite rule as to what kind of abnormality will be present in any particular case. The same is, in general, true of the reflexes. Many years ago, Gowers⁵ pointed out that the manifestations in a patient in coma depend to a large extent on the depth of the coma, whatever the cause may be. If the coma is light,

TABLE 3

PHYSICAL CHANGES HELPFUL IN THE DIAGNOSIS OF COMA AND THE CONDITIONS IN WHICH THEY OCCUR

Odor of breath	
Alcohol.....	alcoholism
Acetone.....	diabetes, uremia
Illuminating gas.....	carbon monoxide poisoning
Color of skin and mucous membranes	
Hyperemic.....	alcoholism
Cherry red.....	carbon monoxide poisoning
Cyanosis.....	cardiac decompensation, pneumonia
Pallor.....	hemorrhage, pernicious anemia
Jaundice.....	choleemia
Local signs of injury.....	trauma, burns, hemorrhage, epilepsy, erysipelas
Temperature	
Increased.....	pneumonia, meningitis, encephalitis
Decreased.....	carbon monoxide poisoning, diabetes
Pulse	
Rapid.....	diabetes, pneumonia, meningitis, eclampsia
Irregular.....	cardiac decompensation
Slow.....	Stokes-Adams disease
Respiration	
Küssmaul.....	diabetes
Increased.....	pneumonia
Hemiplegia.....	cerebral vascular lesions
Observation of convulsions.....	epilepsy, cerebral vascular lesions, central nervous system syphilis, alcoholism
Vomiting.....	cerebral hemorrhage, poisoning
Stiffness of the neck.....	meningitis, cerebral vascular lesions
Kernig's leg sign positive.....	meningitis, cerebral vascular lesions
Chest signs	
Consolidation.....	pneumonia
Fluid.....	empyema, ruptured aortic aneurysm
Pulmonary congestion, ascites, enlarged liver, distended neck veins.....	cardiac decompensation
Distention and spasticity of the abdomen.....	ruptured esophageal varix
	carcinomatous erosion of the gastro-intestinal tract, ruptured ectopic pregnancy, miliary tuberculosis
Muscular twitchings.....	uremia
Abdominal tumor.....	eclampsia
Bulging fontanels.....	meningitis
Soft eyeballs.....	diabetes
Wounds or scars on tongue.....	epilepsy
Vaginal examination abnormal.....	pelvic malignancy, ruptured ectopic pregnancy
Blood Pressure	
Increased.....	cerebral vascular lesions, uremia, eclampsia
Decreased.....	trauma

the reflexes may be preserved and may be hyperactive, perhaps because of release of lower centers by lack of cerebral control. Automatic swallowing may be preserved, and the pupils may still react to light. Painful stimuli may elicit muscular movements. As coma deepens, the depression of the high centers spreads to the lower. Reflexes become diminished or absent, swallowing becomes impossible, the pupils fail to react to light, the body musculature becomes flaccid, and myo-

TABLE 4

LABORATORY OBSERVATIONS HELPFUL IN THE DIAGNOSIS OF COMA AND THE CONDITIONS IN WHICH THEY OCCUR

Lumbar puncture	
Pressure	
Increased.....	cerebral vascular lesions; meningitis; trauma; syphilis of the central nervous system
Decreased.....	diabetes
Bloody fluid.....	cerebral vascular lesions; trauma
Purulent fluid.....	meningitis
Organisms by smear and culture.....	meningitis
Sugar	
Low.....	meningitis
High.....	diabetes
Protein high.....	meningitis; syphilis of the central nervous system
Spinal fluid Wassermann positive.....	syphilis of the central nervous system
Blood examination	
Sugar	
High.....	diabetes
Low.....	insulin shock
Nonprotein nitrogen high.....	uremia
Wassermann test positive.....	syphilis of the central nervous system
Low red blood count, abnormal smear.....	pernicious anemia, leukemia
Culture positive.....	pneumonia, meningitis, septicemia
Spectroscopy.....	carbon monoxide poisoning; methemoglobinemia
Urine examination	
Sugar	
Gross albuminuria.....	eclampsia, uremia, cardiac decompensation
Gastric lavage; examination of gastric contents.....	
poisoning	
Roentgenograms	
Skull fracture across middle meningeal artery in extradural hemorrhage	
Lungs.....	pneumonia; empyema; miliary tuberculosis
Heart.....	cardiac decompensation
Electrocardiograph.....	
heart block; cardiac decompensation	

tatic irritability may be lost. When the palatal muscles share in this relaxation they cause the peculiar stertor that is a familiar indication of the depth of the coma. Even the respiratory center may become depressed so that respiration is decreased, shallow and irregular. The lessened respiratory movements fail to clear the air passages of secretion, which accumulates in the bronchi and finally in the trachea, causing the familiar "rattle" that is popularly and rightly recognized as a frequent harbinger of death.

Recently, studies of the electric activity of the human cortex⁶ have revealed that patients in coma exhibit abnormalities in the electro-encephalogram similar to those seen in normal sleep, but of greater severity. No characteristic differences occur in coma due to the various etiologic agents. By direct study, then, as well as by clinical observation, it can be seen that coma is a state of cortical dysfunction which may be

brought about by many pathologic conditions, but in every case the end-result is essentially the same.

Proper Handling.—A study of the efficacy with which patients in coma were handled was made at this hospital.⁷ In 1933, 1167 patients entered the hospital in coma, and 1101 (94 per cent) were diagnosed correctly on admission. Six hundred and ninety were in alcoholic coma, and 688 of these were correctly diagnosed on admission. Of the 477 nonalcoholic patients, 64 (13 per cent) were incorrectly diagnosed on admission. In the total group of 66 cases, which were incorrectly diagnosed on entry, 47 resulted in death, and it was estimated that in 18 of these, death would possibly have been preventable if a correct diagnosis had been made on admission and appropriate treatment started at once.

In the above group of incorrectly diagnosed cases, the lack of an adequate *history* was largely responsible in approximately 45 per cent of the cases. In 8 cases (12 per cent) an incorrect diagnosis was made because of an inadequate *physical examination*. Five of these cases were considered alcoholic because of tell-tale odor of alcohol on the breath, whereas it developed later that three had severe brain injury with fractured skull, one had a subdural hematoma and one had lobar pneumonia. The failure to examine the eyegrounds in one of the cases resulted in an incorrect diagnosis in a patient with brain tumor. In 2 cases, the diagnosis of subarachnoid hemorrhage in one, and meningitis in the other was missed because the examiner in each case failed to test for a stiff neck.

The failure to take x-rays resulted in incorrect diagnoses in 15 cases (23 per cent). x-Rays are of value in these cases, chiefly as an aid in establishing the diagnosis of coma due to brain injury, through the demonstration of fractured skull. x-Rays of the chest are of diagnostic value in patients with coma due to pneumonia or cardiac decompensation.

In cases of coma of unknown origin, the *lumbar puncture* should be regarded, after the physical examination and history, as the most important diagnostic procedure. In 174 cases in the above series (15 per cent of the total cases) the lumbar puncture was of critical diagnostic significance. Among the cases incorrectly diagnosed, 16 (24 per cent) would probably have been diagnosed correctly had a lumbar puncture been done.

CHART

Coma Routine.—Patients entering the hospital in coma are *emergencies*. A life may depend on the rapidity with which a *diagnosis* is made and *treatment* instituted.

I. *History*.—This is of paramount importance. If no friends accompany the patient, talk to the *ambulance man*. Then send out the *police* or a *social worker*. Inquire especially about: *type of onset, injury, alcohol, other poisons, infections, convulsions, headache, previous illness* (diabetes, kidney trouble, heart trouble, high blood pressure).

II. *Physical Examination*.—Be rapid and thorough. Remember this is essentially veterinary medicine. Your patient cannot help you. Use your *eyes*: Note the patient's color, posture, movements; look for *wounds*, especially in the scalp. Examine the *pupils*, the *eyegrounds*, the *eardrums*, the *throat*. Use your *nose*: Is there an odor to the *breath*—alcohol, acetone, illuminating gas? Use your *hands*: Feel for a *stiff neck*, for *fractures*, for *muscle* and *vasomotor tone* in the extremities, for enlarged *glands*, palpate the *abdomen*, test the *reflexes*. Use your *ears*: Examine the *heart* and *lungs*. Take the *temperature, pulse, respiration* and *blood pressure*.

III. *Röntgen Rays*.—Should be taken while the patient is on the way to the ward, unless the patient is in *shock*, when immediate shock treatment takes precedence over everything else. *Skull plates* should be taken in all injuries, and whenever the diagnosis is not evident. Other plates as indicated.

IV. *Laboratory Work*.—(1) *Gastric lavage* for all poisonings, and severe alcoholics. *Save the contents*. (2) *Catheterize* and examine the *urine* as soon as possible. If reducing substances or acetone is present, and in all diabetics, do a *blood sugar at once*. (3) Do the *routine blood* (red and white counts, hemoglobin and smear). In the presence of infection take a *blood culture*. (4) Take blood routinely on nontraumatic cases for a *Wassermann* and *non-protein nitrogen* determinations. (5) *Spectroscopy, icteric index, van den Bergh, electrocardiograph, blood CO₂, combining power, etc.*, when indicated.

V. *Lumbar Puncture*.—Routine in all injuries (except during shock), *cerebral vascular accidents, convulsions*, in the presence of signs of *increased intracranial pressure* or *meningeal irritation*, and in all cases where the diagnosis is obscure. Note the *initial pressure, color of fluid, red and white cell count* and *Ross-Jones protein test*. Remove enough fluid for *Wassermann, total protein* and *gold solution examination*. When indicated, do *smear, culture* and *chloride* and *sugar determinations*.

The essential practical points which arise from the above discussion have been abstracted and grouped in the form of a chart suitable for display in the hospital admitting room and intern laboratories (see Chart). The *coma routine* thus constituted should be of value in the proper handling of the patient who enters the hospital in coma.

To illustrate how this coma routine works out in actual practice, let us follow it through in a typical case. The

physician is called late in the evening to see a patient who has just been brought into the accident floor of the hospital. The patient is in coma. No friends are present to give a history and the ambulance man who brought the patient in has left. The physician at once instructs the nurse to notify the police that the history in question may be a life or death matter. He then examines the patient. There is an odor of alcohol on the breath. There are contusions and abrasions of the face and hands. Careful examination of the scalp reveals a swelling over the right parietal region. The pulse is 60, the blood pressure 160/90. The examination is otherwise negative.

The patient is sent to the wards by way of the x-ray department and skull plates are taken. Routine blood and urine examinations are made and are negative. The police now bring in the patient's landlady who reports that the patient had come home by himself in the early evening and was obviously drunk. He had apparently been in a brawl since his face was bruised. Inasmuch as this was not an unusual situation for this particular individual, the landlady was not alarmed. An hour or so later, however, she found the man lying stretched out on the floor unconscious. Being unable to arouse him, she called the hospital ambulance.

The wet x-ray plates are examined, but are negative for fracture. A lumbar puncture is done and blood-tinged spinal fluid found under increased pressure. The patient is immediately made ready for operation, largely because of the history of coma supervening some hours after the occurrence of trauma to the head. At operation, a large subdural hematoma is discovered and the patient has an excellent chance for recovery.

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DIAGNOSIS AND TREATMENT OF POLYNEURITIS*

TODAY there are only 2 types of polyneuritis which the physicians of North America need seriously consider. Epidemic beriberi has practically disappeared from this continent and the majority of physicians may practice a lifetime without being called on to treat those forms due to chemical agents, pregnancy, diabetes, and conditioned deficiency states. Therefore, the greater portion of this discussion will be devoted to the diagnosis and treatment of 2 types of polyneuritis only.

These 2 are alcoholic and acute infectious polyneuritis, and the more common of these is alcoholic polyneuritis. Perhaps it is not coincidence that paralysis among alcoholics was well described by John Lettsom¹ and James Jackson² as early as 1787 and 1822 respectively, and that Chomel³ by 1828 had given a vivid picture of an epidemic of polyneuritis in Paris.

These 3 observers had no conception with what they were dealing. Graves,⁴ who had been in Paris at the time of the epidemic and knowing that the pathologists had found no changes in the central nervous system, fifteen years later suggested disease of the peripheral nerves.

ALCOHOLIC POLYNEURITIS

The diagnosis of alcoholic polyneuritis is not usually difficult for the cause of the patient's indisposition is all too evident. Out of the past of one hundred and fifty years ago comes a description on which it would be difficult to improve:

"The first appearance of indisposition very much resembles the gout: and the fuel is heaped upon the fire until the at-

* No contraindication for the use of the word "neuritis" has been found since "itis" is merely the Greek feminine adjectival termination and the word disease is understood. Neuritis therefore means disease of the nerve and not necessarily inflammation.

tachment to the use of spiritous drinks becomes so predominant that neither threats nor persuasions are powerful enough to overcome it. Frequently the appetite for food vanishes but sometimes continues voracious; and at the same time, whilst the body is costive, and no vomiting ensues, the lower extremities grow more and more emaciated; the legs become smooth as polished ivory and the soles of the feet even glassy and shining and at the same time so tender that the weight of the finger excites shrieks and moaning. The legs and the whole lower extremities lose all power of action. The arms and hands acquire the same paralysis and render the patients incapable of feeding themselves.

"Mostly before they die they take less food; sometimes a diarrhea succeeds, sometimes a vomiting of black matter, but most generally they gradually sink from the accumulation of pain and debility. There is rarely any fever. They do not fall into dropsies but usually become paralytic."

If we cannot add to the graphic language of Dr. Lettson's description perhaps we can add a few facts relevant to the history and physical examination.

Neuritis in chronic alcoholics may have a gradual or an acute onset. The first symptoms are numbness and weakness of the feet followed by severe pain and tenderness of the calf muscles. Foot drop and then wrist drop appear and the reflexes are abolished, especially those of the knee and ankle. The sensory loss is most marked in the distal portions of the extremities yet there may be extreme hypersensitivity to pressure over the soles of the feet. Atrophy of the involved muscles soon appears and occasionally edema of the legs and arms. Coarse tremors of the mouth and tongue are almost always present but paralysis of a cranial nerve is rare. Sphincter difficulties are not present.

At times a psychosis occurs. If diarrhea is present over a long period dermatitis follows and determines the diagnosis of alcoholic pellagra, if not, the dementia is termed Korsakov's psychosis. Typical of both mental disorders are confabulation, confusion, memory loss and disorientation.

Acute excitement and depression and delirium accompanied by hallucinosis are more typical of the psychosis with endemic rather than with alcoholic pellagra.

Laboratory studies are usually negative with the exception of gastric acidity. About 50 per cent show diminished or absent free HCl.

The prognosis of a single attack of alcoholic neuritis without psychosis is good but the ultimate prognosis is poor.

Treatment.—Bed rest is essential whatever the severity of the signs and symptoms of polyneuritis. Analgesics and a cradle to keep the bedclothes off the feet may be necessary if pain and tenderness are severe. If the patient is restless or psychotic, paraldehyde is a useful drug. Sand bags and later splints should be used to prevent contractions. When the patient has recovered sufficiently, physiotherapy should be undertaken. Within the last few years a great deal of stress has been laid on the use of a high vitamin diet in this type of polyneuritis. Since the symptoms bear a resemblance to beriberi and pellagra vitamins B₁ and B₂ have been employed extensively. The results of this therapy are extremely difficult to evaluate. In the first place one is dealing with degenerated and degenerating nerve fibers which cannot be hurried in their recovery process. A large number of alcoholic polyneuritides are admitted to this clinic yearly and it is our impression that neither parenteral liver extract, brewer's yeast, nor vitamin B₁ speeds up to any great extent the process of healing in the presence of a severe foot and wrist drop. As an example of the extremely slow rate of recovery in the presence of high vitamin therapy, a patient had a severe alcoholic polyneuritis in 1931 with return of knee jerks within a year. The ankle jerks did not return until January, 1937, though the foot drop had disappeared four years before.

If pellagra is present nicotinic acid should be given. These patients should have a high caloric, high vitamin and easily digestible diet. Concentrated vitamin B₁ therapy should be utilized, especially on incipient instances of alcoholic polyneuritis.

ACUTE INFECTIOUS POLYNEURITIS

For fifty years the greatest of confusion has existed with regard to infectious polyneuritis. The textbooks mention any number of acute infections which may be complicated by a symmetrical multiple neuritis and pay but scant attention to the disease entity, acute infectious polyneuritis. In spite of

this fact let it be said that the former type is extremely rare while the latter is next in frequency of occurrence to the alcoholic type.

As early as the 1860's the syndrome of facial diplegia and weakness of the legs had been described by several authors. Twenty years later it was realized that the clinical picture was that of a polyneuritis, possibly of an infectious nature. In 1908 Laurans⁵ collected 18 instances of this syndrome and during the World War Holmes⁶ and Bradford *et al.*⁷ observed 12 and 30 examples respectively of this disease among the British soldiers in France.

By 1916 Guillain⁸ had observed the characteristic spinal fluid finding, that is, a high total protein without increase of cells. Taylor and McDonald⁹ performed both a lumbar and cistern puncture on one patient and found that with a protein of 206 mg. in the lumbar fluid, that of the cisternal fluid was 49 mg.

The etiology is unknown, though Bashford believed he had transmitted the disease to monkeys. He used an emulsion of cord obtained at postmortem. The pathological anatomy is not spectacular and consists of degeneration of myelin of peripheral nerves with axonal changes in their cells of origin.

Diagnosis.—The onset is usually afebrile with weakness of the legs followed by weakness of the arms and paresthesia of the extremities. The thighs and upper arms are more affected than the feet and hands. Involvement of the trunk muscles is common but the facial diplegia is the most characteristic feature of the disease, though cranial nerves such as the third and sixth may be involved. The deep reflexes are lost. In comparison to the great motor weakness the sensory loss is extremely slight and often amounts to paresthesia only. There are no mental symptoms.

The spinal fluid is of great assistance in diagnosis due to the high protein unaccompanied by pleocytosis. The initial spinal fluid pressure may be raised, accounting for the headache in these instances.

Treatment.—The treatment is largely symptomatic. Complete bed rest is essential. If necessary, contractions should be prevented by splints. A respirator, if one is available, should be held in readiness. If the cerebrospinal fluid pressure

is raised frequent lumbar punctures add to the comfort of the patient. This measure also removes the excess protein and gives valuable information as to the progress of the disease. Prognosis is usually favorable.

ACRODYNIA

A rare form of infectious polyneuritis in children is acrodynia or pink disease. The name acrodynia was first used to describe the symptoms in the 1828 Paris epidemic of polyneuritis, and possibly it was the same disease in adults.

There is a widespread involvement of the peripheral autonomic nervous system with some degeneration of the peripheral somatic nerves. The symptoms referable to the autonomic nervous system are sweating, lacrimation, tachycardia, hypertension, photophobia, abdominal cramps, anorexia and pain and erythema of the extremities. The child presents a vivid clinical picture which, once seen, is not easily forgotten. It lies with the face buried in the pillow in the knee-chest position, constantly rubbing together its reddened desquamating hands. The symptoms referable to the central nervous system are apathy, muscular pain and weakness.

In 7 out of 17 lumbar punctures Blackfan and McKhann¹⁰ found the spinal fluid protein raised (in one patient as high as 250 mm.). Inasmuch as all 17 of these patients were seen late in the course of the disease it is likely that a much higher percentage would have shown a high protein had they been examined earlier. Since the etiology is probably some unknown type of infection, treatment is wholly symptomatic. Most important of all is the nutrition of the child and secondly the use of sedatives such as the barbiturates.

POLYNEURITIS IN PREGNANCY, ACUTE INFECTIOUS DISEASES AND BERIBERI

During both pregnancy and fever the metabolism is raised and often the intake of food diminishes. Therefore a deficiency state such as beriberi may follow. The polyneuritis following hyperemesis gravidarum and that which used to follow a variety of acute infections in the days of "starve a fever" was probably on this basis. Landry's acute ascending paralysis also appears to belong in this group since the poly-

neuritis followed after extreme dietary deficiency and pneumonia.¹¹

Gestational polyneuritis usually follows hyperemesis gravidarum and is thought to be the manifestation of a deficiency state. Clinically it resembles the infectious type of polyneuritis with the exception of the facial diplegia. The motor symptoms are much more marked than the sensory and the proximal musculature may be more involved than the distal. Tachycardia and a psychosis of the Korsakov type occurs frequently. The spinal fluid is negative. Prognosis is poor but if the patient survives the first two weeks recovery usually takes place.

Treatment according to Plass and Mengert¹² is none too successful (8 of the 12 cases died), but they believe parenteral vitamin B₁ should be used. If all else fails the statement that a therapeutic abortion is going to be performed may be successful in terminating the vomiting. Here again, since death is usually due to respiratory failure, a respirator should be in readiness if possible. When recovery is under way preventive methods directed toward the skin, joints and muscles, as previously described, should be instituted.

DIABETIC NEURITIS

Polyneuritis or tabes as a complication of diabetes is so rare that Jordan¹³ reports 120 only out of the thousands of patients attending Joslin's clinic during a three-year period. In fact the so-called "diabetic neuritis" is usually not a neuritis at all but a diabetic tabes with loss of reflexes and position sense in the legs. However, a certain percentage do show the typical picture of an acute polyneuritis of the extremities. There are 4 possibilities suggested as to etiology. First, that the nerve degeneration is due to vitamin deficiency, either dietary or conditioned by lack of gastric secretion. Secondly, that fat metabolism is altered. Thirdly, changes are due to arteriosclerosis and poor nutrition of the nerves. Fourth, that the changes in the nerves are due to an infection.

Without giving the many negative reasons against these various mechanisms let the one positive, constant finding be stated. The spinal fluid protein is high, 37 out of 40.¹³ the more severe the neuritis or posterior column involvement, the higher the protein. In 6 fluids from bed-ridden patients ex-

amined at the Massachusetts General Hospital and the Boston City Hospital, the protein has ranged from 95 to 399 mg. per 100 cc. Three cistern fluids had 36 to 47 mg., showing that the protein arose in the spinal canal. This finding alone removes the disorder from the deficiency and arteriosclerosis groups. Even in diabetic coma the protein is normal. As far as known only tumors, myxedema, and infections give such proteins without pleocytosis. Since there is no question of tumor or myxedema and since the resistance to acute infections is lowered in diabetes, the neuritis or radiculitis may be due to an actual infection. The prognosis for the patients with acute diabetic neuritis is good. In our experience the instances of chronic diabetic tabes have not improved.

It goes without saying that the first rule of treatment is to treat the diabetes first, last and always. Since pernicious anemia and diabetes may occur in the same patient, perhaps because both are due to glandular deficiency states, the gastric juice should be examined in patients with diabetic neuritis. A certain percentage, 30.4 per cent¹³ will have no free acid in the gastric juice, although the number is no greater than in diabetics in general, and these should be treated intensively with parenteral liver extract. The others should at least be tried on liver by mouth and a high vitamin diet, though Jordan did not feel that this group improved any more rapidly on this therapy. Trophic ulcers of the feet are common in this disorder since both an arterial and nerve lesion is usually present. Cleanliness and absence of any friction from shoe or stocking should be stressed to the patient. If an ulcer is present the problem becomes surgical.

POLYNEURITIS IN CONDITIONED DEFICIENCY STATES

Following interference with digestion or absorption of food, a polyneuritis on a deficiency basis may occur. Any chronic diarrhea due to dysentery, chronic ulcerative colitis, gastrotomy, or surgical accidental short-circuiting of the intestine may be followed by a polyneuritis. It is probable that this type is closely related to beriberi, pellagra, and combined systemic disease.

In conditioned deficiency states the clinical picture, of necessity, is not clear cut. When a chronic diarrhea is present

the patient is losing not only all vitamins but the digestive ferments as well. There may be a degeneration of either or both the posterior and anterior columns of the cord as well as the peripheral nerves. Keefer¹⁴ has described 2 patients with dysentery and polyneuritis and Urmy *et al.*¹⁵ mention patients with chronic ulcerative colitis and accidental surgical short-circuiting of the intestine complicated by beriberi. The neuritis in conditioned deficiency states is apt to be limited to the legs and often cord involvement is present. The immediate cause of the nerve degeneration is usually apparent and treatment should be directed toward controlling the diarrhea and replacing the vitamins so lost.

POLYNEURITIS DUE TO CHEMICAL POISONING

When industrial hazards and poisons in proprietary preparations have been removed another variety crops up in some unexpected spot. Polyneuritis from arsenic and lead has practically disappeared since Fowler's solution is no longer prescribed in large doses over long periods of time and since the majority of paints used by furniture manufacturers no longer contain lead. In 1930, just as the heavy metals were coming under control by public health measures, an epidemic of polyneuritis from ingestion of Jamaica ginger broke out in this country. In Europe the same type of polyneuritis was seen following the use of apiol, a drug used to produce abortion. Both Jamaica ginger and apiol were found to contain triorthocresyl phosphate, a poison affecting the peripheral nerves and cord. After this, thallium acetate, contained in a depilatory paste, was found to be the cause of multiple neuritis.

The paralysis due to lead is typically a motor weakness affecting the anterior horn cells of the cervical cord, while that due to arsenic usually affects the sensory portion of all peripheral nerves to the extremities as well as the motor. Clinically it is similar to the alcoholic polyneuritis with extreme sensitivity of the affected parts and the distal musculature more affected than the proximal. An exfoliative dermatitis and a white line across the nails may be present. The cause of these 4 forms of polyneuritis is determined by chemical tests. At present the spectroscopic test of the blood is the most useful in determining the presence of lead. Stippling of the red cells

is usually present. A simple qualitative test for arsenic is the Reinsch test on twenty-four-hour urine specimens. The Gutzeit test is used for a quantitative measurement.

The treatment of the conditions is largely symptomatic though in lead poisoning calcium and phosphorus are given, and in arsenic poisoning intravenous sodium thiosulfate.

SUMMARY

Although it is difficult to distinguish pathologically between the various polyneuritides because secondary degeneration is present in all, a differentiation is more easily accomplished clinically. The types due to arsenic and alcohol involve both the sensory and motor nerves to the distal portions of the extremities. Polyneuritis due to lack, or vomiting of, vitamin B₁ or to the acute infectious type, is more widespread and involves the motor to a much greater extent than the sensory nerves. In the latter, however, facial diplegia is usually present. The groups due to conditioned deficiency states, diabetes, and nerve poisons such as lead, triorthocresyl phosphate, and thallium acetate usually show symptoms referable to the spinal cord as well as the peripheral nerves. In North America the two most common forms encountered are acute infectious and alcoholic polyneuritis.

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PARANOID PSYCHOSIS IN NARCOLEPSY AND THE POSSIBLE DANGER OF BENZEDRINE TREATMENT

ALTHOUGH many cases of narcolepsy have been reported, there have been few which were associated with psychoses.^{1, 2, 3} Three narcoleptic patients with psychosis have recently been seen by us, and are here presented. Furthermore, these 3 cases present certain common features and points similar to the previously reported cases, both in the psychiatric and medical picture. As benzedrine was used in the treatment of narcoleptic attacks in 2 of our cases before the onset of the acute psychotic state, the value of this drug in narcolepsy and its possible action in precipitating a latent paranoid psychosis also warrants consideration. This possible action of the drug assumes more importance because of its somewhat indiscriminate use in a wide variety of conditions: shock, coma, postural hypotension,⁴ falling arterial blood pressure after spinal anesthesia,⁵ smooth muscle spasm of genito-urinary⁶ and gastrointestinal tracts,^{7, 8} barbital poisoning,⁹ fatigue or drowsiness of any cause whatsoever,^{10, 11} and depressive or psychoneurotic states,^{12, 13, 14} besides its prescription in typical cases of narcolepsy¹⁵ and of chronic epidemic encephalitis.^{16, 17}

CASE HISTORIES

Case I.—A thirty-four-year-old white, married man, who had recently become anxious, suspicious and excited, was hospitalized for five weeks in a mental hospital. His family history showed diabetes in one grandparent and an aunt, and goiter in two sisters. His father was eccentric but economically

successful. The mother died of tuberculosis when the patient was quite a small child. Soon after this the home was broken up. His father has remarried three times and neglected and berated the patient for being a failure. He had asthma from childhood and had severe influenza at fifteen and twenty-seven years of age. His sex instruction was minimal. He was occasionally incontinent of urine until the age of twelve. He married at twenty-two and his wife and 3 children are healthy. He was of a friendly, fairly sociable make-up, but tended to mood swings, becoming very enthusiastic about new things, and he was sensitive, attaching undue importance to trivial happenings. His attitude toward his father alternated between love and hate.

His narcolepsy started insidiously during his early twenties with diurnal drowsiness developing into frequent attacks of an irresistible desire to sleep. At about this time he also began to have "collapsing spells," associated with emotion. Because of the occupational hazard he had to change his job several times. Treatment with ephedrine lessened the number of his narcoleptic and cataplectic spells. The cataplectic attacks were accompanied by "chattering" of the teeth and brief lapses of consciousness. In 1933 he was studied by Dr. Fuller Albright who found the following:

1. Physical examination: moderate obesity, weight of 175 pounds and height of 5 feet 9 inches, plethoric facies, and musical râles in chest.
2. Neurological examination: showed no abnormalities except unequal pupils, rather deliberate movements and expressionless face.
3. Basal metabolic rate of -20 and -18 .
4. Mild polycythemia (red blood corpuscles 5,200,000 and hemoglobin 102 per cent Sahli).
5. Low fasting blood sugar (82 mg.) and low sugar tolerance curve which later did not rise after injecting adrenalin.
6. Lowering of blood sugar level by insulin injection to 46 mg. without a sleep attack.
7. x-rays of skull, chest, heart, abdomen, negative.
8. Lumbar puncture, urine, blood, normal.
9. Wassermann test negative. :

The patient commenced taking ephedrine in 1932. Since then he has been noticeably suspicious and about 1935 he became more so, gave up his job and went to another section of the country, hearing plots against his life. In September, 1936.

he ran over and killed a child, the same age as one of his children, and was fined for negligence in driving. He was much upset by this and gave up his job. In January, 1937, benzedrine, 20 to 30 mg. per day, was prescribed for him and in February he occasionally doubled the dose without order. He became tense and anxious, feared for the safety of his family and had ideas of influence. He sought police protection and believed his house wired. His wife persuaded him to consult a doctor and he was admitted to the Massachusetts General Hospital, but that evening became acutely paranoid, fearing that he was being poisoned, and he had to be taken forcibly to the McLean Hospital.

There he became immediately cooperative, but was depressed and paranoid. All medication was stopped on admission and he improved rapidly. He was overtalkative and discursive and at times felt bewildered. Neurologic examination showed only asymmetric face and divergent strabismus. On several occasions his sleep was disturbed by nightmares and he thought there were snakes or an alligator in his bed. Color seemed to have an especial significance to him. His ideas of reference and persecution were never well systematized and faded during his hospitalization. He gained some insight and after five weeks left the hospital. Four months later he was taking no benzedrine and had been able to get a new job as a salesman.

Case II.—A twenty-eight-year-old single man was admitted to a mental hospital in 1935 and complained then of recurrent suspicions for some six years and of sleeping spells and "paralyzing attacks" during the same period. The family history showed only "nervousness" and one alcoholic grandparent on the maternal side. His birth had been instrumental after a long labor but his childhood was normal except for sleep walking. He finished high school uneventfully and after that did laboring work in his father's factory. His interest in girls had been slight. He was described as imaginative and shy, irregular in his output of energy and quite thrifty. His medical history was unimportant except for influenza during 1918 or 1919.

About six years before admission the patient was treated for sinusitis in a hospital and at that time thought that people

were watching him and that he would be arrested. The fears apparently subsided about one month after his return home. About five years before admission he began to have sleep attacks in the day and "terrible visions" with catalepsy at night. These have continued until the present. His paranoid trend has become more marked; he has heard voices whispering about him; he has had ideas of influence and has felt that a group was working against him and his family. His hallucinations had a strong homosexual trend.

Physical and neurologic examinations were negative as were routine laboratory studies of blood and urine. The Hinton test was negative; blood sugar and nonprotein nitrogen were normal; lumbar puncture and x-rays of skull showed no abnormalities; a sugar tolerance test was not done. Two basal metabolic rates were — 10 and — 13. He cooperated well at the hospital but talked with some reluctance about the voices and did not "want to be insane." He seemed only moderately concerned about his condition but was hypochondriacal and preoccupied about sex.

During his five weeks in the hospital he showed no change in his paranoid psychosis, but on 20 mg. of benzedrine sulfate a day his narcolepsy was somewhat lessened. The effect of the drug on the psychosis over a longer period of time could not be observed in the hospital. The patient is at present working part-time and his condition is generally unchanged.

Case III.—A twenty-five-year-old white single man was admitted to the psychiatric service of the Massachusetts General Hospital in 1936 with a history of narcoleptic seizures for the preceding three years and ideas of reference and hearing voices for five weeks. His parents were both unstable; his father was alcoholic and his mother had exophthalmic goiter. His parents were divorced and each remarried, so the patient, practically deserted at the age of four, had been brought up by an aunt and uncle. They treated him well and gave him an education; during his present illness they observed him closely.

The patient was disturbed by the quarrels of his parents and had chorea as a child. In adolescence he was lonely and introspective. He was a good student, majoring in philosophy and psychology at college but (after the onset of the present

illness) failed in graduate study, showing more interest in the experimental animals than in the required work. After leaving the university he wandered at loose ends through several jobs and hobbies, showing no sustained interest and energy in these and at times getting into difficulties with his superiors. He used alcohol occasionally to "pep him up." He had one serious affair with a girl, but generally tended to fall in and out of love quickly and was much preoccupied with the subject of marriage. He had probably never had sexual relations. The patient had always been self-centered and anxious to make a good impression; he seemed to have too high an opinion of his own mental powers. He tended to be suspicious and indecisive. Recently he has become resentful, tactless and argumentative.

In November of 1932 the patient noticed that he was unusually sleepy and that when emotionally upset, he would suddenly feel weak. He became irritable and short-tempered. About a month later he had an attack of "influenza" which was ill-defined. The cataleptic seizures were associated with some convulsive movements of the neck muscles, but, there was no loss of consciousness. They increased in number until April, 1933, when he had as many as 50 a day, later diminishing and responding to large doses of ephedrine sulfate, which also helped to control his drowsiness. Neurologic examinations and study in 1933 were negative except for low basal metabolic rate (-19 and -11) but the patient began to fear that he had either brain tumor or epilepsy and thought the doctors were withholding information from him. About two months before admission his former sweetheart was killed in a skiing accident.

Six weeks before admission he started on a new job and worked very hard. At the same time he substituted benzedrine sulfate for ephedrine and probably took it in larger doses than those prescribed. Although he felt tired after one week he became exhilarated and self-conscious, thinking that people were noticing him and later that they were calling him a "homo." The hallucinations increased and frightened and confused him; eventually he appealed for help to his doctor who he believed might be controlling the voices.

Physical examination showed slight obesity and rather flabby musculature. Pupils were small, slightly irregular and

reacted poorly to distance. Deep reflexes were lively and equal. Blood serum bromides were 75 mg./100 cc. on admission, later showing only a trace. Basal metabolic rate tests were — 10 and — 13. Other studies, including blood counts, urine, Hinton, blood sugar and nonprotein nitrogen, lumbar puncture, and x-rays of skull were entirely negative.

Mentally he was alternately affable and irritable; depressed and appreciative. At times, he was demanding, suspicious, threatening and trying to escape. He often appeared preoccupied and bewildered. He was overactive and occasionally reacted to hallucinations. His talk was fragmentary and circumstantial. He told of his hallucinations, that people were accusing him of sexual crimes and of his delusional ideas that the doctor would torture him and emasculate him. His trend was homosexual and paranoid but not systematized. During his three weeks' hospitalization he became more at ease, although he impulsively smashed a pane of glass. He was convinced that the "voices" were real, arguing that otherwise he must be crazy; that was the extent of his insight. His hallucinations continued during his hospitalization and have persisted for over a year after discharge, yet the patient has been able to work on a farm and do work as a salesman for short periods. He consults his physician occasionally telling him, "Oh, yes, I hear the voices but they don't bother me much"—then somewhat irritably, "Can't you stop them, doctor, I believe you could—you may be sending these people after me."

DISCUSSION

In reviewing the literature relating to psychoses with narcolepsy we cite the cases reported by Brown,¹ Schilder² and Daniels.³ Brown's case was of a nineteen-year-old boy with typical narcolepsy. Physically he was obese. The psychosis was characterized by hallucinations and delusions of persecution, by confusion and bewilderment, periods of violence and homicidal tendency and by failure to recover. There was no history of encephalitis.

Schilder's patient was a twenty-nine-year-old male with typical narcolepsy of fourteen years' duration and ideas of reference of nine years' duration. The family history revealed that his 2 sisters were excessively large. The patient had

enuresis until the age of ten, and had slept with his father until the age of fifteen. Other past history is irrelevant. He attributed his drowsy spells to masturbation as they followed closely upon a masturbatory episode. His ideas of reference consisted in the belief that people were calling him a homosexual and would breathe hard when they were near him. Physically he was tall and heavy but well proportioned, being 6 feet 5 inches tall and weighing 250 pounds. His skin was pasty; his body hairy and he had a feminine escutcheon. Neurologic examination was negative. Basal metabolic rate was -20 and sugar tolerance curve was delayed but otherwise normal. x-Ray of skull was negative. Mentally he was clear, discussed his paranoid ideas and brought in both heterosexual and homosexual dreams. Besides psychotherapy he was given caffeine, thyroid and pituitary extract. His drowsiness was somewhat relieved and he gained some intellectual insight into his delusions. Schilder called attention to the presence in narcolepsy of latent homosexual and paranoid trends.

Daniels' case was a thirty-four-year-old woman who had somnolence and cataplexy for seven years and who became suspicious of her husband and those about her. Her narcolepsy and suspicions ran a somewhat parallel course with remissions and later progression to Parkinson's syndrome.

It is not surprising that 5 of the 6 cases were in men as most authors report a larger incidence of narcolepsy in men than in women, Daniels giving a ratio of 2:1.

We consider it significant that all these 6 cases of psychoses with narcolepsy show a paranoid form. All cases show either suspiciousness, delusions of reference or persecution, or jealousy. Three show more definite evidence of a strong homosexual trend, *i. e.*, 2 of our cases and Schilder's case.

Careful study of patients with narcolepsy brings out evidence which suggests that there are endocrine and metabolic changes. The most common findings are:

Case I: Obesity, plethora, polycythemia, lowered basal metabolic rate, all to a slight degree; increased sugar tolerance with a failure to rise after adrenalin; and a high resistance to an insulin shock reaction.

Case II: Slightly low basal metabolic rate; carbohydrate studies were not done.

Case III: Obesity and low basal metabolic rate; carbohydrate studies were not done.

Schilder's case likewise showed endocrine abnormalities.

The hallucinatory-paranoid psychoses described by German authors^{18, 19, 20, 21, 22, 23} as occasionally associated with chronic encephalitis are somewhat similar to the ones above presented and might suggest an encephalitic origin for our cases of psychosis with narcolepsy, but evidence of this is inconclusive, particularly as not all encephalitic psychoses have this picture. Furthermore, it must be realized that the type of mental symptom is more probably determined by the patient's past life than by the location of the inflammatory lesion in the brain: the encephalitis may release abnormal reactions but just what sort of behavior is released may be psychologically determined.

Review of the literature on benzedrine shows that although it is a recent drug, the present state of knowledge of its action has been fairly well described. Its peripheral action is sympathicomimetic, lessening smooth muscle spasm and raising arterial blood pressure;⁶ its central action produces exhilaration and restlessness with relief from the feeling of fatigue;¹⁰ it dissipates sleep and drowsiness. Also it lessens cataplectic phenomena and is used in narcolepsy where it is three times as effective as ephedrine.¹⁵ When benzedrine is used in the psychoses (manic-depressive, depressed cases) and psychoneuroses where depression or fatigue is a prominent symptom, it may relieve these symptoms or it may have an unwished for action by causing insomnia, and anxiety, sometimes accentuating delusions of guilt.¹² In 2 of our cases (I and III) it may have precipitated the psychotic reaction; the onset of the psychotic symptoms coincided with benzedrine medication and these patients showed great apprehension amounting to panic, together with confusion and bewilderment. One patient had delusions and the other auditory hallucinations; these symptoms persisted after the benzedrine had been discontinued. One might describe the probable psychologic action of benzedrine as follows: The patient becomes more alert and observant; when extreme, this leads to ideas of reference and misinterpretation. Thus in patients with a latent paranoid trend, as appears to be the case in some narcoleptics, a psychosis may be precipitated.

In Case II and in the cases already reported, psychotic symptoms had supervened when no benzedrine had been given, so that benzedrine could not be incriminated as a precipitating factor in those cases. Benzedrine prescribed during the course of the psychosis did not modify its form or course in Case II.

CONCLUSION

We have described a specific paranoid psychosis in three cases of narcolepsy. Three more cases have been reported elsewhere. The psychoses as well as certain endocrine-metabolic disturbances are similar to those described in the German literature as following encephalitis. Benzedrine appeared to be a precipitating factor in 2 of our 3 psychotic patients. For this reason, a careful psychiatric examination is indicated before starting benzedrine therapy on narcoleptic patients. If a paranoid trend is discovered, it may be wiser to allow the sleeping spells to continue.

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TRAUMATIC NEUROSES

THE question of the relationship of trauma to the various neuroses, especially in situations involving the law, is a hotly debated one, both in the courtroom and in considerable of the medical literature. It is unfortunate for any scientific subject when it becomes a matter of social controversy and thereby evokes a range of social attitudes.

Thus, there are certain physicians in every community who seem to believe that any trauma, however slight, may precipitate and even cause the most persistent and widespread of the disorders classified under the neuroses. On the other hand, there are physicians who do not seem to credit the reality of any other diseases than those that are of so-called "organic" nature, and dismiss as imaginary or worse the headaches, dizziness, changed mood and altered personality conspicuously present in the neuroses. This is not at all surprising, however, when one takes into account that all litigation represents battle, and in battle people are lined up on opposing sides regardless of shades of opinion and inner qualms of doubt. Furthermore, the neuroses of ordinary practice are even yet dismissed contemptuously as the product of imagination and exaggeration by many hard-boiled physicians who have grown up in the school of organic pathology.

Legal Background.—Since both law and medicine meet in the majority of the neuroses which become of importance following trauma, it is necessary for the physician to know the attitude of the law regarding the responsibility for disease and disability following accident. I am, therefore, stating the main features of the laws as they operate throughout the United States and particularly in Massachusetts. In part the laws turn away from the realities of the situation as represented in

medical thought and against the advantage of the plaintiff or injured party, and in part they lean toward his case and cause, thus favoring him.

In the first place, no emotional shock or, to put it more broadly, no resulting disturbance in mood or mind is valid legally as a cause for recovering compensation or damage, unless there has been physical damage associated with it. Thus, if an individual is tremendously or injuriously frightened by a fire which has taken place near him, unless he is struck by falling timbers or has stumbled and struck himself; or has been wet down by water; or has inhaled an appreciable and damaging amount of smoke; the result is not compensable even if it takes the form of the most permanent neurosis. If, however, the individual has been injured, no matter how slightly, then the attendant emotional circumstances also come into play, but the critical emphasis is always laid on the physical blow or damage.

Moreover, if in an accident, someone near and dear to the individual has been killed before his eyes—as a brother, sister, father, mother, wife, husband, or child—and there has been deep psychic damage as a result, this is not compensable and must be excluded from the situation as part of the injury done to the plaintiff. His emotional disturbances, in other words, are strictly limited in their scope; they must relate to himself, and not to anyone else. Thus, in a case recently seen by me, a boy who had been shaken up in an accident developed a neurosis, but when this was studied, it was found that his depressed mood and his altered personality related to the fact that his brother had been killed in the same accident, and that he felt quite wrongly that he had been responsible for his brother's death and was haunted both in his waking and his sleeping hours by the reproaches of his conscience. This artificial dissociation undoubtedly serves adequate and proper legal purposes, but it obscures the medical aspects of the situation and leaves too much room for hair-splitting statements which can, in fact, be only slightly better than guesses.

The American law leans toward the plaintiff, however, in those cases where there exists preexisting disease or constitutional predisposition. It is the postulate of the law that accident and injury take a person as he is, and that if he is 67

the verge of a fatal disease, and an accident hastens his demise, no matter how little, the total responsibility of his death rests upon the accident or injury. If it is abundantly clear that the patient has a predisposition to mental or nervous disorder, and if a trauma pushes him over, so to speak, into a neurosis or psychosis which was undoubtedly on its way, the trauma is, nevertheless, held to be an aggravating or precipitating factor, and is given the total responsibility for creating the disease, in the sense that full compensation may be received on this ground.

Situational Nature of the Traumatic Neuroses.—The neuroses which follow accident or injury are further complicated, so far as the medical and legal evaluation of the situation is concerned, by being in a partial sense at least situational neuroses. This term has long been known in medicine. It merely means that under the pressure of a set of circumstances, an individual becomes lowered in energy and endurance, changed in mood and personality, and experiences various disagreeable or fear-inspiring reactions in his body, which are brought about, insofar as our present-day notions of etiology are valid, by the emotional situation and other stresses. Obviously, a neurosis which develops in relationship to litigation and compensation has a different situational background than one developing under other circumstances, although in the main its general aspects are the same and its symptomatology may be in no important way different.

In the first place, an accident is, almost by definition, an intrusion in a direful way of the *unexpected*, and thus is a blow to security. A man walks into a place of business, falls down a trapdoor into a cellar, and lies there partly conscious, and suffering greatly from emotional and physical injury. In certain individuals, this event operates to destroy the feeling that the world is a solid place, where one may put his foot without fear of impending disaster. A man drives along a highway; he knows that there are accidents, but he has a full sense of confidence in his ability to control its (and his) destinies, regardless of the operations of others. Suddenly a machine swings out of line and crashes into him. The solid feeling of safety and self-confidence disappears; fear and anxiety enter into his life, so that driving a car becomes an ordeal charged

with mental and bodily disorder. However an accident happens, it is unexpected, and the surprise and shock disorder that sense of certainty and security which is the basis of normal, non-neurotic conduct.

Secondly, an accident may dislodge an individual from his social security. It may throw him out of a job; it may render him incapable of earning adequate wages; it may alter his plans for the education of his children and the purchase of his home. All these sum up as injury to his egoism, and injuries to the egoism have long been recognized as valid causes for neuroses.

Thirdly, a sense of injury and resentment may develop. The law, as Hamlet pointed out, is a tedious and slow instrument for the obtaining of justice. However inevitable its tediousness and delay may be, cases drag out. The injured person may feel that he has an immediate right and an immediate need to be compensated for his injuries. Instead he finds a cold reception on the part of the opposing side. The implication that he may be a faker may also poison his emotional state, so he builds up a semiparanoid attitude, finding discriminating injustice, where in fact none exists, since what he has to endure may be inevitable in an orderly scheme of things. Though in certain of the legal situations, such as in the Industrial Accident Boards and the veteran and pension bureaus, the legal and medical alignment is supposed to be impartial and to be seeking to do justice to the injured man as rapidly as possible, this rarely is the case. As a matter of fact, due to the fact that malingering does occur, and also to the fact that a lawyer is valuable to an insurance company insofar as he holds down the awards, and a pension agent or a commission member is valuable insofar as he lessens the expense to the tax-payer, battle actually takes place. Moreover, the social alignment into classes, with its inevitable range of prejudices and hates, appears as a factor. This involves an emotional response on the part of the injured person which is certainly unfavorable to a neurosis and its recovery.

Fourthly, the excessively soft and sympathetic attitudes which at times predominate, play an important and adverse rôle. During the earlier part of the post-war period in the United States, compensation was given to veterans for diseases

usually entirely remote from trauma and war situations, such as feeble-mindedness, dementia praecox, manic-depressive psychosis and general paresis, and veterans with neuroses were given education and training for which they were entirely unfitted, and inevitably failure was added as a factor in the prolongation of the neurosis. The halo of heroism which surrounded the returned veteran brought about efforts in his behalf, and pressure was exerted which damaged him, in that it pauperized his spirit, his initiative and his energy, so that he lay back, more or less comfortable, receiving compensation throughout his life for conditions which had little to do with the war.

Fifthly, in industrial situations the unemployment which has been prevalent throughout the world and certainly in the United States for nearly a decade has operated unfavorably against the recovery of an individual suffering from a neurosis. Feeling himself incapable of going back to a full-time job, no matter how improved he might be, and knowing quite well that he could get no job for which he was fully adequate, he remained totally incapacitated so that he might not be thrown onto charity, relief, and the various agencies which help sustain those no longer capable of self-sustenance. (These and other psychologic factors are important to keep in mind in the matter which we are considering here.) This is especially important in the case of the middle-aged and elderly workman who feels that he is no longer quite capable of doing his work, and who sees the ever-threatening specter of sudden discharge from employment awaiting him. The increased liability of the middle-aged man to accident and injury has rendered it quite certain that he will be unable to get employment if he loses his job, largely because of the attitude of the insurance companies themselves, since the rates for industrial accident protection to any employer are dependent upon the record of his factory, shop or place for employment. Therefore, when an accident happens to a middle-aged, or elderly workman, unconsciously he feels the great insecurity that threatens him should he recover. The motivation for recovery is no longer present and, in fact, recovery is an economic damage to him. This brings about a situation in which it would be futilely idealistic to expect the full cooperation of the injured.

Thus, from the injuries which occur in industry, in war, in federal and state employment, and in relationship to the tort or common-law trauma, such as the automobile collision or accident, there arise situations in which neuroses come about not only from the damage actually sustained, but also from the flow of social and psychologic consequences which are, in many instances, of slight importance, but in other cases, of great and perhaps determining nature.

When we turn to the type of neuroses which may follow accident or injury, we are brought face to face with a wide diversity of classifications with which I shall not, in a detailed way, trouble the reader.

Classification of Traumatic Neuroses.—Most of the classifications of the neuroses are altogether too subtle and too particularized for a subject which is still in some respects not sharply defined. Therefore, it is wiser to adopt a more simple classification. The one here advanced bears some resemblance to that of Wechsler, but differs in that the unconscious is studiously neglected, since I do not believe that any valid technics exist for disclosing it. Furthermore, even if psychoanalysis is a valid instrument for reaching into the unconscious and evaluating the situation, very few studies of traumatic situations have been made by this method, and most of the assumptions are based upon a general attitude rather than a specific knowledge of the traumatic cases.

I. The group of postconcussional states, that in which a syndrome of headache, dizziness, and lowered energy and endurance is the main result of the accident or injury. Secondly there may develop, owing to the situational factors, a wide variety of symptoms which will be found discussed in more detail under the subsequent headings. Oppenheim and others have assumed that there is actual organic, although diffuse and almost ultramicroscopic, damage in these cases, and it is very likely that there is some damage of an organic type. To this organic substratum there are added the symptoms and manifestations of the neuroses.

II. The traumatic neuroses proper, that is, the group of neuroses in which visceral and physical disabilities play the most important rôle, and corresponding more to neurasthenia. In these cases, profound mental symptoms are not conspicuous.

although in some measure these are always present. In this group of cases, the complaints present the bewildering pattern of the neuroses of everyday practice. Elsewhere, I have attempted an orderly description of the symptom groups which may be summarized as follows:

(a) A disturbance in the sense of energy and endurance which characteristically is greater in the morning than in any other part of the day, and which may reach an extreme degree. This disturbance is not associated with any physical signs which adequately account for it.

(b) A disturbance in the capacity to rest and recuperate, so that instead of the restorative effects of sleep, there are effects which seem quite the reverse, whereby the individual awakes from sleep more tired than when he went to bed. Furthermore, the ability to sleep is lessened, so that insomnia of one type or another is quite commonly complained of. The restlessness of this type of patient is shown in many ways and, in general, fatigue instead of breeding a rest-desiring state brings a restless feeling.

(c) There is a failure of the various types of appetites, including those for food, sex, social relationships and work of any coordinated type. Purpose and ambition, which are higher developments of appetite, become correspondingly disturbed.

(d) There is a marked overreaction to stimulation which is probably a fundamental disturbance. Normally, the body has not only a capacity to react to stimulation but also a capacity to limit and even exclude stimulation. There is, so to speak, a conserving inertia which acts as a shock absorber and buttresses the integrity of the organism by preventing the multitudinous stimulations from interfering with the orderly visceral processes. In the neuroses, the heart becomes disturbed; it may be too rapid or obtrude itself into consciousness, whereas normally its action is unconscious. So with spasms, dilatations, and disordered motility of the gastro-intestinal tract. Every other organ of the body may become involved in a specific way exclusively, so to speak, or as part of the general hyperreactivity. Thus, there develops tremor, flushing, tachycardia, even hypertension, gastric, pyloric, and intestinal spasm, and frequency of urination. Concomitant with this hyperresponse of the organism are the paresthesiae which appear in various

parts: the pressure on the back of the neck, the tight and bandlike feelings, the blurred vision, the tinnitus, the bad taste in the mouth, the curious prickly, numb, and formication sensations.

(e) As the patient fixes his attention upon these symptoms, he becomes hypochondriacal. Fear of his physical integrity develops. He becomes introverted and tends to retreat from contact with others and from those situations, namely, the crowd, the church, the game of cards, the theater, which ordinarily are pleurably exciting, but in these cases bring pain and paresthesiae rather than pleasure. These paresthesiae and visceral disturbances are the essence of the neuroses of this type. I do not believe that the individual creates them by his attention. I think his attention is fixed on himself by their occurrence. Whole groups of cases of this type have been isolated, as the tachycardias, the spastic constipations, the neuroses of the bladder, and of the sexual structures, such as nervous impotence and hyperirritability. This whole group has been classed by some as representing "irritable weakness." Something occurs by which the organism becomes overresponsive, with the result that the neurosis imprints itself by disordered visceral function. Untoward emotional states are present; anxiety occurs. In fact, there are no pure forms of neuroses; but in the typical posttraumatic neurosis of this group, the patient is well preserved in his personality and his emotions are not too irrelevant, although he is depressed, fatigued and anxious.

III. The third group may be classified as the traumatic anxiety states. The symptoms which are detailed above may be present. The overreaction to excitement, stimulation and noise is certainly and usually present. There develop, however, marked phobias which may be situational in type but are usually more or less universal in their nature. There takes place an incapacity to be alone or to cross the street or to enter a movie. Some particular reaction becomes fixed in the mind, such as a feeling of nausea, and consequently the individual fears that any situation will arouse this nausea, lead to vomiting, and bring about disgrace or the discomfiture of public attention to a socially inappropriate act, and the consequent inferiority of the patient will be stressed or publicized.

Similarly, fears are associated with the bladder and rectum. This anxiety also takes the form that one will become unconscious, when subject to stress or strain, and be picked up as the unknown stranger. A typical anxiety state is that which is commonly seen when the individual awakens from a sleep, finds his heart racing, so he becomes covered with sweat; he may turn red or pale, according to his type of vasomotor reaction, thinks he is going to die, as does his family at the first instance. The fear of the attack, even the fear of the fear, becomes part of a chain of anxiety difficult to break into and constituting one of the most formidable problems in the whole of psychiatry. Every event not only casts a shadow before, but projects by its mere contemplation a paralyzing and distressing terror. There is consequently a retreat and the individual clings to his own home, which becomes the place of safety.

It is quite probable that this type of reaction is largely constitutional and not to be placed mainly at the door of the accident or injury. The rôle of the constitutional state or of previous experiences, whichever view one chooses to take, plays an important rôle in the anxiety states. I think, however, it cannot be denied that the emotional perturbation of an accident or injury, together with its consequences, may intensify an anxiety neurosis already present or precipitate, in some measure, one probably predestined to occur. One can amplify the types of anxiety reaction to include all the situations the individual may find himself in, and thus exhaust the Greek prefixes to the word phobia. One may also exhaust the visceral responses which take place in fear and dread, and find them all exemplified in this condition.

IV. A fourth type of neurosis very commonly and very disconcertingly present is the traumatic hysteria or dissociation type. Traumatic hysteria is prevalently a male disease, because men are more subject to trauma than women, and occurs quite frequently in sturdy, solid looking laborers with no past history. The range of dissociation is that of ordinary hysteria. Any function may be dissociated from consciousness, so that there is hysterical blindness, deafness, aphonia; hysterical nausea, vomiting, diarrhea; hysterical amenorrhea or dysmenorrhea; hysterical impotence or priapism, etc. There may be

hysterical paralysis involving a hand, a total extremity, and half the body, usually excluding the face. The types have been well described in the literature and need no amplification here. It is this type which is more associated with malingering than any other.

V. The traumatic personality disorder: all of the types described above in a broad sense show personality disorder. The specific disorder which is here described is that which Adolf Meyer first singled out. After trauma there develops that semineurotic and semiparanoid personality which no longer can adjust to work, play, social relationships; which develops into a walking encyclopedia of bitter reproaches to society, especially as represented by courts and insurance companies. Litigiousness appears, and since the desire for compensation is never fulfilled in anything like adequate measure, there is a resentment shown in all the contacts of the individual, an increasing solitariness because he exhausts the patience of those who sympathize and try to help him out. Often plausible, he evokes the sympathy of others, but as they attempt to help him, they find themselves more and more baffled, frustrated in their efforts by his reactions, his lack of tact and his exaggerated bitterness. The exaggeration of symptoms, the inconsistencies of manifest strength as compared to the complaints leads to the uneasy feeling that the individual is somewhat dangerous and quite disgusting. There can be no doubt that certain severe injuries to the brain produce personality alterations of this type, although actual brain damage is more apt to produce dementia or lowered intellectual capacity than the paranoid attitude. But very often trifling accident and injury plunges the *predisposed individual* into a cycle of events and conflicts, as a result of which his symptoms increase and his hostile reactions involve larger and larger segments of the world. The patient's reactions usually do not quite reach the stage where they may be called psychotic, where actual delusion-formation is present, although this may occur. Social and vocational disability usually becomes complete and permanent.

Malingering.—The important question of malingering presents itself wherever litigation is involved. Here we must differentiate, as many of the authors do, between the exaggera-

tion and the so-called "unconscious" malingering of hysteria and the neuroses generally, and true malingering. To the normal, healthy man it seems exaggerated that a patient who complains so vividly of so many symptoms of all kinds is capable of walking, talking and even of working. The pains are alleged to be imaginary or exaggerated, because no organic basis can be found. The physician should be humble in this respect when he contemplates the history of medicine. Many disorders, in which pain and disability appear, were declared functional until an organic pathology was found or a disturbed physiology was disclosed. Conversely, if pallor and flush can be caused by emotion, there is no reason to assume that a pain in a part may not be produced by the same machinery. If reversed peristalsis and spasm of the gastro-intestinal tract may be of "psychogenic" origin, there is no reason to assume that a similar cause may not account for headache and dizziness. The shift in circulation, which is so remarkable in the normal mental states of fear, anger, disgust, surprise, fatigue, etc., may also be postulated as disordered when these emotions become exaggerated as in the neuroses.

However, malingering may be postulated when conscious lying in important matters is discovered. Thus, if a patient under repeated questions fails to tell of a previous attack or previous accident, or says that he has been in bed continuously when, as a matter of fact, he was in bed for a short period of time or not at all; if what he tells is directly demonstrable as a lie, it is safe to say that he is lying in other respects as well; and if the symptoms are disproportionate to the trauma, that he may be declared to be malingering. Unconscious malingering is too vaguely understood to be seriously taken into account. Conscious falsification is another matter, and I think it should be a rule for experts and courts that where there is definite falsification present that the case as a whole is built on lies, the subjective symptoms may be minimized or disregarded, and malingering assumed to be present, at least in large measure.

Some authors have stated that malingering is part of a neurosis. I do not believe that this is true in ordinary civil practice. In all neuroses, the actual disability is less than the patient believes it to be, but on the whole he does not falsify

the situation more than can be expected of fallible human beings, normal or mentally sick. Real malingering may be psychopathic, as some claim is to be, but I prefer to call it greed and criminality.

Prognosis.—It is curious that the unfavorable prognosis of many of these cases is stressed in the literature, as if that unfavorableness were something unique or particularly related to the traumatic neuroses and not to the neuroses in general. As a matter of fact, the organic, objective diseases are often more treatable, more hopeful than many of the neuroses. It is my opinion that the difference in prognosis between the non-traumatic neuroses and the traumatic neuroses has been greatly overstressed, as if they dealt with essentially different matters. Everyone in the practice of medicine knows the cases that drift unhappily from hospital to hospital and from doctor to doctor vainly seeking relief, even after the formidable technic of psychoanalysis, as well as the more modestly advanced therapies of other types. In fact, it is the difficulty with the treatment of the ordinary neuroses which accounts for the power of the so-called "cults."

It is probable that the cases in which trauma and then litigation enter present a somewhat worse prognosis than do the other conditions, although in my opinion the statistics in the matter are inadequate and do not include a sufficient range of cases, as for example in the statistics, so often quoted, of Schaller, in which the total number of cases seems to have been 47 divided up into 5 categories of payment, nonpayment and type of payment compensation. Most of the writers, however, agree that the prognosis in the compensation cases, that is, the case of the industrial accident type, or the type which is to receive pension, is improved if an early settlement of the case is reached, and very likely this statement may be made of tort cases as well. Prolonged litigation is good for lawyers and experts only, but is probably an injury to the patient. This does not mean that the patient recovers immediately upon the payment of compensation, or when the case is settled by trial, whatever its termination may be. I think, on the whole, it may be said that this ameliorates the situation and makes recovery more easy. It does not in itself end the symptomatology. The

patient may no longer so frequently visit the doctor and usually does not, but this does not necessarily mean cure.

In many of my cases the patient has gone back to work but has done so perforce of circumstances and against a residual disability, just as many people in private life continue to work because activity is more tolerable than inactivity, although their symptoms persist in formidable degree. It is not, I think, true that gold is a panacea for the traumatic neurosis.

Treatment.—The treatment is that of all the neuroses, whether in private practice or in relationship to law and litigation. (1) Remove, if possible, the disconcerting, disturbing emotional situations. (2) Enlighten the patient insofar as his mentality is capable of appreciating this enlightenment as to the nature of his symptomatology. (3) Sleep, endurance, appetite, visceral disorder should be treated by appropriate pharmacologic, physical and hygienic measures. Since this is not a paper on the treatment of the neuroses, I shall not discuss details. Drugs, however, are of value, just as much as psychotherapy. In fact, psychotherapy is, like many another noble gesture of man, more honored in the breach than in the observance thereof, even where competent medical attendance in this respect may be obtained.

Very few cases have been psychoanalyzed and thus treated by this means, so that there is no real avenue of therapy in this direction. It is probable that psychotherapy consists fundamentally in the change of environment, social stabilization insofar as this is possible, ending of litigation if this can be done, and the establishment of a psychologic relationship between doctor and patient, by which the patient obtains confidence and assurance in himself, as well as in his physician. Too long a dependence upon the physician or upon any agency of help should be discouraged, although no brusque or cruel method is possible in our society as at present constituted. It is possible, of course, that such means as were used during the war, torpillage, by which painful electric currents were given to the bodies of hysterics, may produce results just as in private practice at the present time spectacular results are still obtained in isolated instances by the use of what may be called legitimate "hocus pocus."

All therapy has to take into account at all times the social

level and the general personality of the individual. Enlightenment may be of value in some cases; it is of little value in those cases unable to appreciate what is said. More primitive means of restoring function and confidence often must be used. The history of the neuroses is the history of "cures" by the electric current, by cruelty, kindness, shrines, osteopathy, chiropractics, Christian Science, psychoanalysis, tincture nuxvomica, and sodium bromide as well as benzedrine sulfate and phenobarbital—all of which means that as yet we are not masters of the treatment of the neuroses, whatever their genesis—whether by trauma or by the less spectacular strains of life.

The literature on this subject is enormous. The World War, the development of industrial accident boards, the increasing range of pension bureaus of all types, as well as the huge increase in accidents which parallels the intrusion of the automobile on the highways have brought with them an immense literature in all languages on the traumatic neuroses. I here refer to some of the more important writers:

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ELECTRICAL INJURIES TO THE CENTRAL NERVOUS SYSTEM

INTRODUCTION

THE manifestations of injury from industrial and domestic electric currents may be divided into those which are acute and those which are late.

Concerning the *acute or initial cerebrospinal symptoms* we know that especially in injuries by currents of higher amperage, unconsciousness occurs, which lasts hours or days, and is frequently complicated by motor irritation, such as jactational hyperkinesis and epileptic or myoclonic convulsions. These symptoms, including unconsciousness, may either follow the electric shock immediately, or after an interval of a few seconds or minutes, during which the victim may be conscious. In this stage, disorders of peripheral circulation have been observed, such as pallor, or more frequently cyanosis. Jellinek described cases in which unconsciousness occurred immediately after the electric shock, followed by convulsions and states of delirium and confusion. In some of these cases he found increase of intracranial pressure, and in those which came to autopsy, cerebral edema. One of Jellinek's patients, after receiving a shock of 5000 volts, fell down immediately. Circulation and respiration had apparently stopped. Ten minutes after being revived by artificial respiration, he developed a severe raging excitement, which lasted two hours, after which time he became unconscious again, and showed generalized hyperkinesis with trismus and opisthotonos, later tonic-clonic convulsions. The pupils were narrow and did not react to light; the Babinski sign was present on the left. An hour later the patient was clear and conscious again. Another patient, after recovering from his initial unconsciousness ran around

aimlessly for awhile, delirious and confused, then suddenly dropped dead.

These severe initial symptoms after electric shock are by no means dependent upon passage of the current through the brain. Biemond described a case in which the current had passed from the right hand through the legs to the ground. A short time later the patient became unconscious; and after recovering consciousness, developed vomiting and headache, monoplegia of the right arm, hypersensitiveness of the right side of the body and choking of the disk on the right. All of these symptoms cleared after thirty-three days. Biemond considered them as due to an acute edema of the brain following the electric shock.

This case and others suggest that the cerebral sequelae of electric injuries in most instances are not due to direct tissue damage, but are indirectly transmitted to the brain by circulatory disturbances. Jellinek has recommended lumbar puncture for the relief of increased intracranial pressure in such cases, in addition to prolonged artificial respiration, and has carried it out with success.

Late and permanent manifestations of injury of the central nervous system are rare, but do occur. In their patchy distribution they often resemble multiple sclerosis. The commonest are the atrophic flaccid paralyses, often taken for neuritides. Cases of hemiplegia, of hemiathetosis, of myoclonus of the facial musculature, oculomotor, pupillary and vestibular disorders have been reported. Several instances of a parkinsonian syndrome, amnesia and various organic psychoses are recorded.

CLINICAL PRESENTATIONS*

Case I.†—Male, forty-two years old. Encephalomyelitis with spastic atrophic paresis of arms and legs and cord bladder, following electric injury by high tension alternating current (60 cycles; 8000 volts; 1–10 amperes).

* The electro-technical data regarding the following cases have been interpreted to the author by Mr. A. Weeks, to whom the author wishes to express his indebtedness.

† The attending physicians in this case were Drs. Allan L. Davis, Charles G. Freed and Arnold N. Allen, in consultation with whom the author saw and examined the patient in the hospital and after his discharge. The author is indebted to them for permission to utilize data of their examinations.

A healthy, well-developed, forty-two-year-old white male, on the morning of October 22, 1936, at 4.30 A. M. while removing a faulty transformer at a dairy plant, came in contact with one of three live leads (drop wires), which had been disconnected from the faulty transformer and were hanging down from a 13,800-volt Y-connected power line. The patient had stepped with the left foot upon the cement foundation of the transformer, which was 18 to 20 inches above the ground; his right foot was still on the ground; his left hand was on the transformer; in his right hand he held a new hemp rope, with which he was about to put a lash over the top of the transformer. While stepping with his left foot on the base of the transformer, his head either touched one of the drop wires or came close enough to one of them to establish an electric contact. The voltage to ground from any of these drop wires was 8000 volts; and this is the voltage to which he was connected first, through his head, with which he had established the contact. This flow of current was intensive enough to ionize the air in the neighborhood of the patient sufficiently to cause a 3-phase short circuit between the 3 dangling drop wires, which subjected the patient, who stood amid them, to flow of additional current besides that through the point of first contact, through his head and chest, to both hands and to the left foot and from either of these 3 points to the ground. The amperage of the entire 3-way short circuit, which was measured, was 300 amperes; an estimate of the amperage to which the patient was exposed is difficult, on account of the partially indirect contact by arc; it may be estimated at from 1 to 10 amperes. He received severe burns on both his hands, the front of his chest, his face, upper arms, right knee and left foot; he fell down unconscious, though not sufficiently hard or from sufficient height to cause additional injury by falling.

At 10.30 A. M. he was transferred to the Boston City Hospital. Examination revealed third degree burns in palms of both hands; first and second degree burns over both upper arms and the upper part of his chest; first and second degree burns on face and scalp. There were first and second degree burns on the right knee, and a dry ulcer the size of a dollar piece on the sole of the left foot (Fig. 72). This ulcer showed all the characteristics of a specifically electric lesion: it con-

sisted of a slightly blood-tinged excoriation, which felt hard, and was surrounded by a small, elevated, whitish ridge. The surface was dry and there was no secretion and no surrounding redness.

The other skin lesions were so complicated by burning that they appeared essentially as burns; in all probability they were due to one or more high tension sparks at the various points of entry of the current. In this regard, it was also interesting to



Fig. 72.—Current marking. Case I. Exit of current at left foot. (Photograph taken one week after the injury.)

note that the rims of his eyeglasses were outlined by corresponding burns about his eyes, indicating entrance of the current by sparks at these places. The specifically electric lesion of the left sole represented obviously an exit of the current.

There was no discharge or bleeding from the external auditory canals, the nose, or the mouth. The pulse was 70 to 100 beats per minute; the blood pressure was 120/78; the temperature 99.2° F.; respiration 22. There was no cardiac enlargement, no signs of hardening of the arteries. Motility, tonus

and sensation of body and extremities were unimpaired; the deep and superficial reflexes were normal; there were no pathologic reflexes, especially no Babinski or Gordon and no ankle clonus. The contents of the urine were normal, as were the blood chlorides, the nonprotein nitrogen, the hemoglobin content and the cellular elements of the blood: hemoglobin, 90 per cent; red blood corpuscles, 4.5 million; white blood corpuscles, 19,200, polymorphonuclears, 80; lymphocytes, 15; mononuclears, 5. On the third day (October 24) sugar appeared in the urine,* but no other pathologic contents.

During the night of October 24, the patient became restless at 11 P. M., then confused, delirious, cursing loudly and disturbing the ward. His temperature during the night rose to 100.4° F. He was quiet the next day. On October 26, that is on the fifth day after the injury, at 5 P. M. he complained for the first time about numbness in his legs; but the motion was still unimpaired. At about the same time, he also complained of headache. On the morning of October 27 (the sixth day after the injury), he also developed weakness in both arms and legs: he had become unable to lift his knees easily and his hands dropped when elevated passively. There was also marked hypesthesia, almost anesthesia from the groin down. Babinski sign was now positive on the right.

The neurologic consultants found, on the afternoon of the same day, that his pupils were regular, equal and reacted well to light and accommodation. The disk margins were hazy and there appeared to be slight edema of the heads of the optic nerve on both sides. There was horizontal nystagmus bilaterally, but this was ascribed to the medication (barbital). There was weakness of all extremities, in the legs more marked than in the arms. Babinski sign was positive on both sides. There was hypesthesia for pain and temperature from L5 down. The vibratory sense was lost from D2 down; touch was intact throughout. There was beginning retention of urine. Lumbar puncture showed initial pressure of 250 cc. of water (patient well relaxed); the dynamics were normal. The fluid was slightly bloody, of yellow color, no clots. It contained 1080 red blood corpuscles, no white blood corpuscles.

* As in a case of Balkhausen and Grueter, injured by alternating current at 25,000-volt tension

Total protein was 26, sugar 65, chlorides 630; colloidal gold curve 0011100000. The diagnosis of encephalomyelitis, following electric injury, was made.

Owing to retention of urine, the patient was placed on tidal drainage. Cabot splints were applied to the feet in order to counteract the sequelae of the foot drop. The patient became restless, noisy and irrational at times, especially at night.

Repeated lumbar punctures which showed pressures varying from 310 to 260 cc. of water appeared to relieve the cerebral symptoms. The paraplegia persisted, but sensation gradually returned. His reflexes became hyperactive and Babinski was positive bilaterally. There was good scar formation over arms and neck; no infection or sepsis.

On February 1, more than three months after the accident, he was visited and examined at home through the courtesy of Drs. Allan L. Davis and Arnold N. Allen, and the following findings were made: the patient was bedridden; unable to sit up, stand, or walk without help. Mentally, he appeared mildly euphoric, seemed to feel much better than his obviously poor physical condition would warrant. He was well oriented, however. There were some memory defects in regard to the original accident and period of hospitalization at the Boston City Hospital. Judgment was perhaps slightly defective in that he felt he would be able to go to work very shortly. According to Dr. A. N. Allen, the patient was difficult to handle at home, and was irritable with nurses.

The cranium was essentially normal except for scars of old burns. The pupils were equal and regular, reacted well to light and accommodation. The fundi were now normal. The lower facial musculature on the left showed slight weakness. There was atrophy and weakness, associated with spasticity, of all 4 extremities. The first finger of the right hand was ulcerated and showed trophic disturbances in the bone and soft tissue. The highest level of muscle weakness was at C₇ or at the deltoids. The patient was unable to lift his arms over his head, and there was marked weakness of the musculature below the deltoids. All extremities were definitely spastic, the legs more than the arms, and the right more than the left. The tendon reflexes were hyperactive. There was bilateral Babinski, unsustained ankle and patellar clonus bi-

laterally. Sensation to light touch and pain appeared generally intact. There was, however, impaired vibratory and position sense in both lower extremities. The left gastrocnemius and soleus muscles were more severely atrophic than the rest of the musculature and also showed fibrillations.

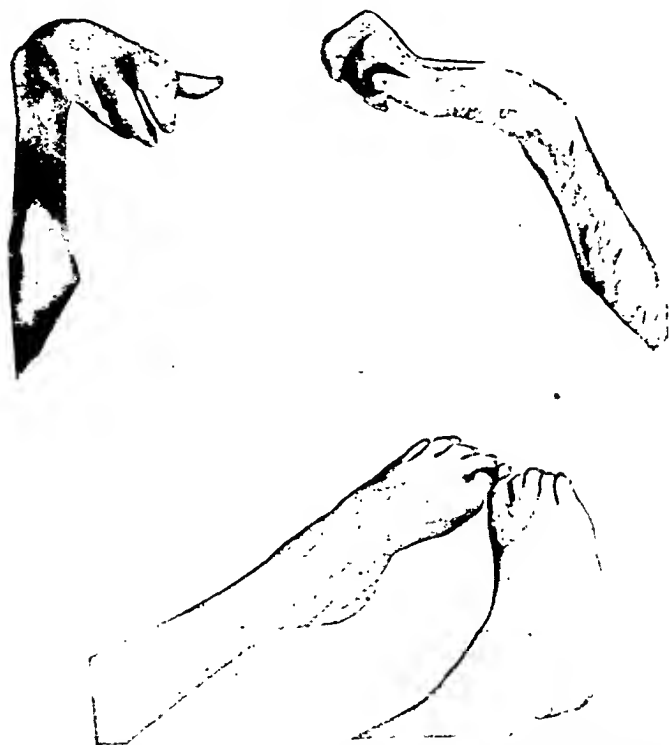


Fig. 73.—Case I. Contracture deformities of hands and feet, secondary to damage of spinal cord. Photographs taken one year after the injury. Note clawhand deformity on left, fallhand combined with clawhand deformity on right, plantar flexion and adduction of both feet.

In November, 1937, one year after the accident, the patient was reexamined by the author several times. The patient was bedridden and unable to walk, stand, or sit up without help. He presented the picture of a spastic-atrophic paresis of arms and legs with contracture deformities of both hands and feet, sensory disturbances, slight weakness of the lower left side of the face and anisocoria. A slight diminution of spon-

taneous activity of facial expression, slight lack of mimicry (in spite of the presence of euphoria) and prolonged course of elicited mimic responses suggested, in addition, a beginning slight change of parkinsonian type.

The fundi appeared normal. The right pupil was wider than the left, and the right pupil was not quite round. The light reaction on the right was sluggish and not quite complete, on the left prompt and complete. The reaction to accommodation, on the right, was not quite complete. The external ocular movements were normal. There was slight lower facial weakness on the left. The tongue could be protruded straight. The musculature of the neck was undisturbed. The arms, from the deltoids down bilaterally, showed weakness, atrophy and spasticity, increasing in distal direction. Hands and fingers showed contracture deformities: the right presented a combination of fall and clawhand, the left showed clawhand deformity (Fig. 73).

Though atrophy and spasticity had remained unaltered, the weakness and the diminution of range of motion had improved somewhat since the last examination. Voluntary movements of shoulders and elbows were possible without limitation of range though with definite weakness. The patient was now able to lift his arms over his head. Biceps and triceps were weak, but the range of motion was undisturbed. In the wrists, bilaterally, weakness as well as severe limitation of active voluntary motion was found. Flexion of wrists was good bilaterally; extension, however, was almost abolished on the right, slightly diminished on the left. Adduction-abduction was abolished on the right, preserved on the left. Pronation was preserved bilaterally. Supination was diminished on both sides, on the right more severely than on the left. The fingers were incapacitated still more severely than the wrists. The only possible voluntary movement of the right thumb was a feeble adduction; the other finger of the right hand could carry out slight flexor and extensor movements of the first interphalangeal joints, but no voluntary motion of the metacarpophalangeal joints or of the end joints of the phalanges was possible. With the left hand, feeble adductor and flexor movements of the thumb could be carried out, as well as slight flexor and extensor movements of the metacarpophalangeal joints of the

other 4 fingers. The interphalangeal joints of the lateral 4 fingers of the left hand could not be moved voluntarily. Purposeful synergic movements of either hand were abolished. Both arms and hands showed spasticity, as well as considerable atrophy. The measurements were as follows:

	Left arm	Right arm
Upper arm.....	21.6 cm.	21.6 cm.
Forearm.....	23.2 cm.	22.2 cm.

Triceps reflex and radius-periosteal reflex were exaggerated bilaterally. The pectoral muscles were weak, but their strength

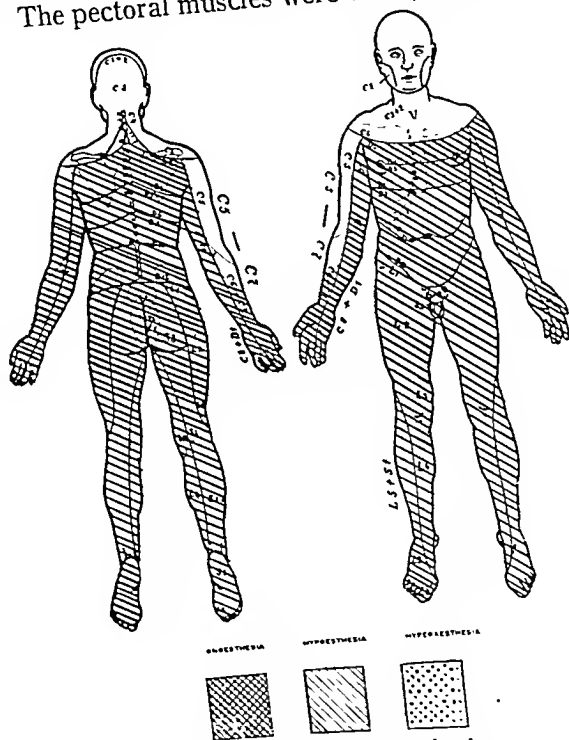


Fig. 74.—Two-point discrimination.

Figs. 74-78—Case I. Diagrams of sensory defects one year after the injury.

was better than that of the other arm muscles. The intercostal muscles and the diaphragm were undisturbed. The upper abdominal reflexes were present and equal bilaterally.

The legs were almost completely paralyzed; only very slight active voluntary motion was possible in both hips, less in both knees, still less in the right foot; the left foot was completely

paralyzed. Slight motion (flexion and extension) could be carried out with the big toe of the right foot, none, however, with the other toes, none with the toes of the left foot. The musculature of thighs and legs was atrophic; the atrophy of the calves was more severe on the left than on the right. The measurements were the following:

	<i>Left</i>	<i>Right</i>
Thighs.....	42.5 cm.	42.5 cm.
Calves.....	25.4 cm.	26.4 cm.

Both legs showed considerable spasticity; in hip and knee joints equally marked, in the left ankle joint less marked than in the right. The feet showed contracture deformity (plantar

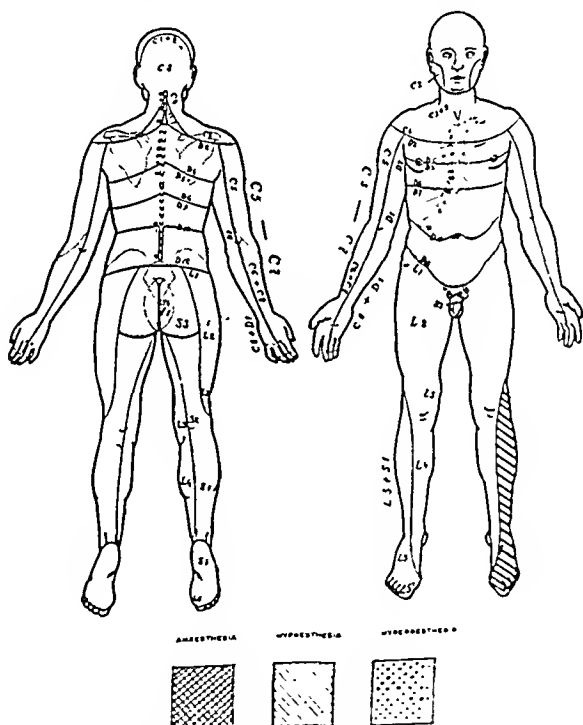


Fig. 75.—Sensation of touch, examined with the brush.

flexion and adduction) (Fig. 73). The knee jerks were extremely and equally exaggerated on either side; brisk responses could not only be elicited by the slightest tap with the reflex hammer, but even by a gentle tap with the examiner's fingertip

at the patellar tendon and proximal from the patella. Patellar clonus could be elicited equally well on either side. The ankle jerks were exaggerated, on the right more than on the left. Ankle clonus was present on the right. Babinski was positive bilaterally; the response of the tensor fasciae latae was active on either side; on the right, the great toe responded by dorsal flexion, on the left no movement of the great toe could be

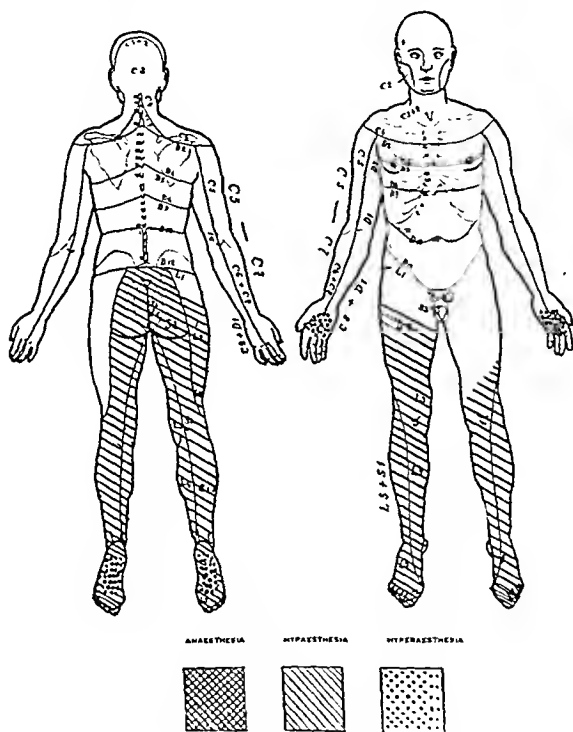


Fig. 76.—Pain and temperature sensation.

elicited. Gordon's, Oppenheim's, Rossolimo's and Mendel-Bechterew's reflexes were negative.

Sensory examination showed severe impairment of all epicritic types of sensation, while protopathic sensation was only slightly disturbed. Two-point discrimination was severely impaired from C₇ down on the right, from C₅ down on the left (Fig. 74). Sensation for touch, however, as examined with the brush, was intact over most of the body; only the fifth lumbar dermatome on the left showed hypesthesia for touch

(Fig. 75). Sensations of pain and temperature (Fig. 76) were quite well preserved, especially subjectively; but from L_2 downward on the right, and from L_3 downward on the left, in many instances, wrong answers were given; when the patient concentrated his attention, the performance was somewhat better. The palms of both hands and the soles of both feet were hyperesthetic for pain (Fig. 76). Position sense was abolished in toes, ankles, knees, hip joints, fingers and wrists, abolished in toes, ankles, knees, hip joints, fingers and wrists,

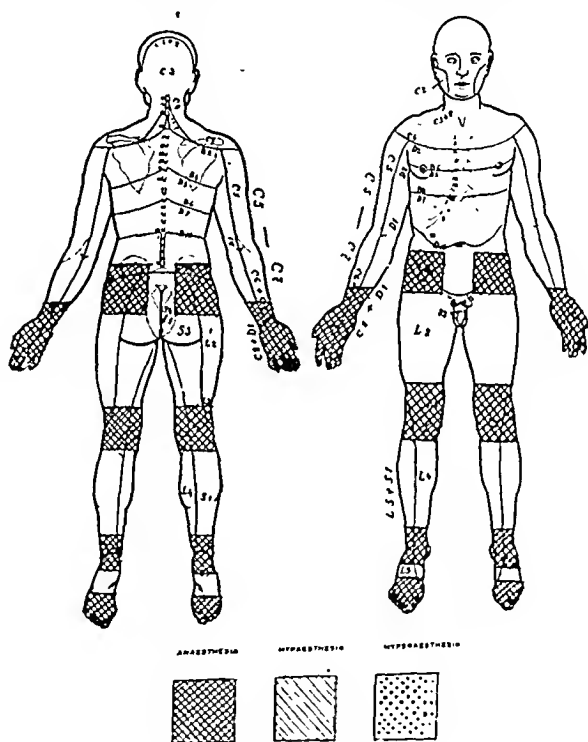


Fig. 77.—Position sense.

but was intact in elbows and shoulders (Fig. 77). Vibratory sense was only slightly diminished at the malleoli, but even here had remained quite adequate; it was intact everywhere else (Fig. 78).

The further development of the case is being followed up.

Discussion.—The picture at present is very similar to that which one might find with a cervical hematomyelia (with the addition of small lesions in the left anterior horn at L_5 – S_2 , in

the left posterior horn at L₅, in the supranuclear left facial pathways, in the periaqueductal gray matter and in the basal ganglia), but the pathogenesis is probably dissimilar. Unlike a traumatic hematomyelia, such as resulting from a fall or a blow, which comes on immediately following the trauma, the cord symptoms in this case did not come on until five days after the trauma. They were associated with cerebral edema, such as evidenced by increased intracranial pressure and choking of

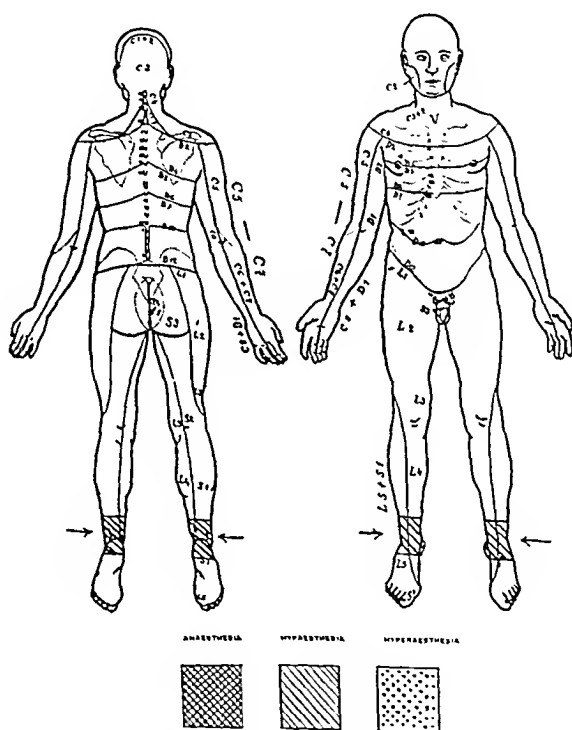


Fig. 78.—Vibration sense.

disks: and with extravasation of small amounts of blood into the subarachnoid space, obviously related to stasis or thrombosis of superficial pial vessels; and had been preceded, on the third day following the accident, by cerebral symptoms. This delayed onset of permanent damage to the nervous tissue is characteristic of electrical injuries and apparently due to vascular alterations which are initiated by the passage of current through the blood vessel walls, especially the intima.

The resulting circulatory disturbance may be assumed to have produced a picture consisting of numerous perivascular necroses, resembling an acute disseminated encephalomyelitis, for this appears to be the characteristic histologic result of venous or capillary thrombosis. At the same time also a marked cerebral edema with increased intracranial pressure was observed, obviously related to circulatory disturbances within the brain tissue, especially the white matter, which is a typical occurrence in encephalomyelitides of other etiology also.

Case II.—Male, forty-six years old. Muscular atrophy, involving the fifth, sixth and seventh cervical segment on the left, following electrical injury by low tension direct current (115 volt, 25 milliampere).

A healthy, well-developed, well-nourished forty-six-year-old white male, on the evening of December 21, 1935, in a dark room was screwing an electric light bulb into the socket of a hanging lamp with his right hand, holding the socket with his left. He remembers that the pullchain of the lamp was dangling against the metal base of the bulb and against his right hand; he may even have pushed it into the socket by mistake. He suddenly felt an electric shock in his left hand, with which he held the socket. He was able to remove his left hand immediately from the socket and noticed that he had received a burn on the end of the fourth finger of his left hand. The current, a direct current of 115-volt, must have passed from the left arm to the right arm, since he was standing on a wooden chair, and thereby well insulated from the ground. The estimated amperage was 25 milliampere. The patient estimates that the electric shock which he had received was only slight, as compared to others which he had experienced at work; but he had never burnt himself before by electric current. The patient went to bed that night without thinking much of the accident. When he awoke the next morning, however, he noticed pain and weakness, almost paralysis, of the left arm. During the following three weeks, the pain did not improve, and often woke him up at night. The weakness became definitely worse. For these reasons, he came to the out-patient department of the Boston City Hospital on

January 12, 1935, three weeks after the injury. He stated that lately he also had noticed quivering (fibrillation) of the muscles of his left upper arm.

Examination showed that the left upper arm was $1\frac{1}{2}$ cm. smaller in circumference in largest diameter of biceps than the right. The skin over the left shoulder and the left upper arm was loose, the muscles flabby and weak. Pain could be reproduced by pressure over the brachial plexus or by forced motion of the head of the humerus in either direction. The result of the sensory examination was equivocal, tending to a moderate hyperesthesia of left upper arm, not radicular in distribution. Pectoral, biceps and triceps tendon reflexes were active and equal. There was no evidence of involvement of the cervical sympathetic. There was a circumscribed, sharp-edged, elevated, dry, hard skin lesion of yellowish color, measuring 3 to 4 mm. in diameter, at the mediodorsal side of the fourth finger of his left hand, close behind the posterior ridge of the fingernail. This lesion in its appearance was identical with the current markings described by Jellinek. α -Rays of the arm and cervical spine did not reveal any pathological changes, especially no bony changes and no changes suggestive of arthritis. The diagnosis of "neuritis from electric shock" was made, and the patient was treated by radiant heat, massage and motion.

During the following three weeks, the patient stated that the pain had become worse; it always began in the scapular region and radiated down into arm and fingers. Examination revealed that there was also more atrophy than was evident at the time of the first examination. On August 30, 1935 (eight months after the injury), the patient was reexamined. The scar from the current marking was still visible on the mediodorsal side of the fourth finger of his left hand, behind the posterior ridge of his fingernail; it was now, however, soft in consistency and on the same level as the rest of the skin, the elevation having disappeared. According to the patient, it had been healing by crumbling off. The patient stated that the pain in the left arm had been gradually improving and had disappeared, but the weakness of the left upper arm had remained unchanged or may have increased slightly.

Examination revealed no pathology of the internal organs

or of the cranial nerves. There was atrophy and weakness of the muscles of the left shoulder and the left upper arm; the bony outlines of the left scapula and of the greater tuberosity of the left humerus protruded (Fig. 79), and the inferior angle of the left scapula protruded slightly. The atrophy and weakness of the left shoulder and arm affected the following muscles: the deltoids, pectoralis major, serratus anterior, infraspinatus, supraspinatus, biceps and triceps (Fig. 79). The

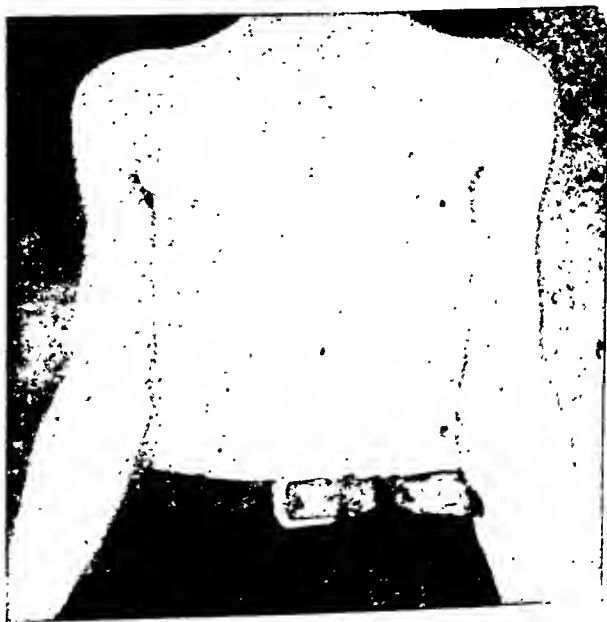


Fig. 79.—Case II. Male, forty-six years of age. Muscular atrophy, involving fifth, sixth and seventh cervical segment on the left, following electrical injury by low-tension direct current (115 volt, 25 milliampere). Photograph of patient taken eight months after the injury. Note atrophy of the *Mm.* deltoideus, pectoralis major, supraspinatus and biceps on the left.

tonus of these atrophic muscles was decreased. Strength, volume and tonus of the muscles of the forearm appeared normal. The following measurements of the circumference of the arms at the points of largest diameter were taken:

	<i>Right arm</i>	<i>Left arm</i>
Upper arm	26 cm	22.5 cm
Forearm	25.7 cm	25.4 cm

It must be emphasized here that the weakness of the atrophic musculature was only of a moderate degree and actually much less severe than one would expect in the presence of the rather marked loss of volume by atrophy. Although the left arm and shoulder were definitely weak, they had retained enough serviceable strength for manipulations not involving excessive force.

The biceps and triceps reflexes were somewhat less lively on the left; the radius periosteal reflex and Mayer's reflex were normal and equal on both sides. Examination of the musculature and nerves by faradic and galvanic currents showed a slight quantitative reduction of the muscular response of the atrophic group of muscles on the left, but no reaction of degeneration. There was no tremor, no ataxia, no sensory disorders, and no tenderness of nerve trunks. The abdominal reflexes were normal and equal. Volume, strength and tonus of musculature and reflexes of the lower extremities were undisturbed.

The picture which the patient presented now was that of a pure muscular atrophy, due to involvement of the lower motor neurons arising from the fifth, sixth and seventh cervical segments on the left, without sensory involvement. This muscular atrophy was associated with weakness, decrease of tonus, and with occasional fibrillations. Although a radicular involvement, especially at the beginning of the patient's disability, cannot be excluded, the picture at the present time is best explained by pathological changes involving the anterior horn of the cervical spinal cord on the left, extending from the fifth to the seventh cervical segment. It is highly probable that the direct current, which had been flowing from arm to arm, had passed this region of the spinal cord, causing at first only vascular changes, such as prolonged vasoconstriction, vasoparalysis, and stasis and thrombosis in the smallest branches of a small group of blood vessels which, during the night following the trauma, led to increasing anoxia of the tissue, sufficient to damage the neural parenchyma in that region, including probably one half of the spinal cord and its roots; the vascularity of the two halves of the spinal cord being quite independent of each other. Whether the pain present during the earlier period following the trauma was due to involvement

of the posterior roots or of the posterior horns of the spinal cord cannot be decided. According to Foerster, pain may be produced by lesions of the posterior horns of the gray matter of the spinal cord.

During the past two years, the picture presented by the patient has remained essentially stationary. At no time was the question of compensation involved. The patient, considering the accident his own fault, had at no time even attempted to get compensation for it. The involvement being on the left, and sparing hand and forearm, he had been able to take up work soon after the accident and to carry it on with only slight discomfort and inconvenience due to weakness of his left upper arm.

Panse has collected and described a number of similar cases.

Case III.—Male, thirty-four years old. Atypical parkinsonian syndrome with mental changes, following electric injury by alternating current of intermediate voltage (45 cycles, 600 volts, 300 milliamperes).

A healthy, well-developed, well-nourished thirty-four-year-old white male, a street car motorman, who had never suffered from any major illness in the past, received an electric shock of 600 volts when changing a headlight, the casing of which by faulty insulation was connected with the incoming powerline carrying a 600-volt alternating current of 45 cycles. The probable amperage that passed from both his hands (with which he grabbed the casing of the headlight) to the ground was 300 milliampere. After the shock, he fell down unconscious and immediately developed myoclonic convulsions of the face. The pupils were constricted and their reaction to light was almost abolished. He regained consciousness after about twelve hours, then was drowsy, incompletely oriented, and at times delirious and excited. He had retrograde amnesia for the accident. The myoclonic convulsions in the face, which involved the facial and masticatory musculature on the left side more intensively than on the right, persisted. In addition, during the half year following the injury he gradually developed tremor at rest, and rigidity and loss of associated movements of the right hand and arm.

During this same period of time, the mental changes be-

came more definite and finally remained stationary. He showed decrease of spontaneity, mental dulness, slowness, unproductivity, circumstantiality, disturbance of memory for recent events, stereotyped uniformity, tendency to iterations and perseverations, cataleptic behavior, difficulty in finding words, disturbance of acoustic attention, paranoid delusions and tactile hallucinations. There was, apart from rigidity and tremor, weakness and adiadochokinesis in the right arm, diminution of tendon reflexes on the right.

The picture remained essentially unaltered during the period of three years during which he was observed at frequent intervals; the left pupil, which had been wider than the right for two years, later became narrower again; both pupils remained irregular. There was disturbance of convergence and nystagmus on fixation on both sides and bilateral exophoria.

As anatomical substratum of this syndrome, small multiple lesions in the brain stem, especially the midbrain and in the central white matter of the hemispheres, were assumed.

PATHOGENESIS

An electric current (alternating current of 60 cycles) of $\frac{1}{2}$ to $\frac{1}{3}$ of a milliamperere is felt by human beings as a "tap"; one of $\frac{3}{4}$ of a milliamperere as a pinch; one of 1 milliamperere as a grip; one of 5 to 15 milliampères causes an unpleasant stimulation of the musculature; one of 15 to 19 milliampères and above stimulates and at the same time paralyzes, or rather blocks, for voluntary motion, the muscles and nerves through which it flows, at least for the duration of the flow of the current; one of 25 milliampères and above may produce permanent damage, especially to nervous tissue and blood vessels; and one of 70 to 90 milliampères and above may be fatal. Since the amperage of the current is the quotient of the voltage divided by resistance, the fatal voltage may be remarkably small, even as low as 25 volts, if the resistance is sufficiently lowered by perfect contact and long duration of flow of current. The resistance of the human body decreases with increased perfection of contact; with increased time of duration of contact and of flow of current, and with increased voltage; it varies from 50.000 to 218 ohms.

The two main causes of death in immediate connection with an electric trauma are: (1) cardiac failure, and (2) respiratory failure, usually associated with vasomotor failure. The cardiac failure may have two causes: (*a*) ventricular fibrillation by direct peripheral action of the current upon the heart; (*b*) inhibition or arrest of the heart by excessive stimulation (central stimulation) of the vagus nerve, especially of the centers of the vagus nerve in the medulla oblongata, this excessive stimulation of the vagus usually being followed by a prolonged though not permanent disturbance. The respiratory and vasomotor failure is always due to paralysis of the respiratory and the neighboring pressor centers in the medulla oblongata.

In laboratory animals the situation is fairly simple. Currents of low tension and intensity kill by inducing ventricular fibrillation (closing of the current arresting the heart, its opening being followed by the ventricular fibrillation); currents of high tension and intensity kill by bulbar respiratory paralysis.

It has often been assumed that cardiac (ventricular) fibrillation occurs in human beings also. Jellinek has, however, pointed out that the occurrence of ventricular fibrillation following electric shock has never been proved by actual direct observation in human cases. He emphasized that death from electric shock is not immediate, but delayed and slow; that the state of apnea and of apparent standstill of circulation following electric shock is due to prolonged but not permanent paralysis of the respiratory, vagus and pressor centers in the medulla oblongata; and that during this period the individual remains viable and resuscitable for a surprisingly long time, provided that artificial respiration is started as promptly as possible and is adequately carried out for a sufficiently long period of time (up to ten or twelve hours).

If artificial respiration is not carried out, the individual dies during the period of bulbar paralysis from anoxemia and from edema of the lungs and the brain.

Practical experience is definitely in favor of Jellinek's point of view. In groups of workers, who are well trained in the prone pressure method of artificial respiration, and who keep it up for sufficiently long periods, the recovery rate from electric shock is high; it is 67 per cent, or 323 successful resus-

citations among a total of 479 cases according to MacLachlan's thorough study. In a group of cases in which artificial respiration had been started before the lapse of three minutes after the shock, the recovery rate was 70 per cent (361 cases); in the group in which artificial respiration had been started at four minutes or more, the recovery rate was 58 per cent (118 cases). The same applies to shock from lightning. MacLachlan also emphasized the fact that success in resuscitation may follow many hours' work on an apparently lifeless victim. He describes an important case (22,000 volts from head to hands and legs), in which the patient was successfully revived after eight hours of prone pressure resuscitation (Sharpey-Schäfer's method), which was carried out uninterruptedly by shifts of trained workers.

The local injury by electrical current is apparently due to prolonged vasoconstriction, followed by vasoparalysis leading to formation of parietal and occluding thrombi and to necroses of vessel walls which are followed by immediate, insidious or delayed necrosis of tissue, usually preceded by edema.

Simple hardening of the arteries of arteriosclerotic type with hypertension has also been observed following electric shock, in one interesting case limited to those parts of the body which had been passed by the current. Jellinek also considered the possibility that workers in plants with electric machinery, who are frequently exposed to minor subliminal electric shocks, and who are more or less constantly working in electromagnetic fields, may show an increased and early incidence of arteriosclerosis. However, this has not been confirmed experimentally.

PATHOLOGY

The general autopsy findings in cases in which the current had passed through the trunk including the heart, and who died in the acute stage following the injury, are edema of the lungs and passive congestion of spleen, adrenals and kidneys. The brain shows edema with flattening of the convolutions, narrowing of sulci and swelling of the central and convolutional white matter: venous congestion and formation of early red thrombi in cerebral venules, small perivascular hemorrhages by diapedesis (Fig. 80). and perivascular lesions of demyelina-

tion and incomplete necrosis which in their distribution and morphology resemble those of an acute disseminated encephalomyelitis (Fig. 81). These may be the morphologic substratum of the encephalomyelitic syndrome observed in our



Fig. 80.—Case IV. Female, forty years of age. Accidental electrocution by handling ultraviolet lamp with faulty insulation while sitting in bathtub (alternating current of 60 cycles, 119–120 volts, 300 milliamperes, from left hand to ground). Section from central white matter of parietal lobe of brain, showing perivascular hemorrhages. Stain: hematoxylin-eosin Photomicrograph (enlargement, 57 \times).

first clinical case, of the localized damage of one anterior horn of the fifth, sixth and seventh cervical segment of the spinal cord, observed in our second clinical case; and of the atypical parkinsonian syndrome presented by our third clinical case. It should be emphasized, however, that no pathologic exam-

inations of the central nervous system in cases of late disturbance of the central nervous system have yet been performed.

The cause of death in cases which are fatal in the acute stage immediately following the injury is obviously circulatory dysfunction; an extreme contraction of the heart associated with generalized arterial vasoconstriction, followed by inhibition of the heart and vasoparalysis is the most likely chain of events. Whether this inhibition of the heart was associated with ventricular fibrillation or whether it was simple inhibition

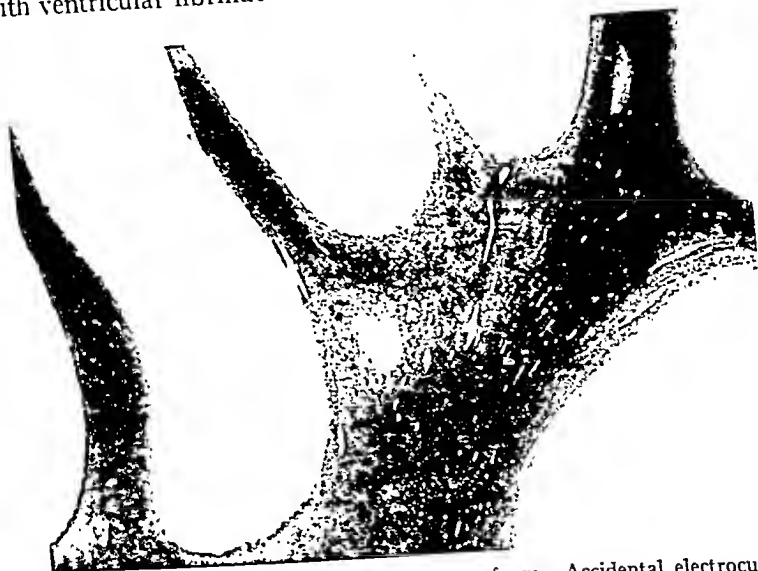


Fig S1.—Case V. Male, seventeen years of age. Accidental electrocution by heating pad of faulty construction (alternating current of 60 cycles, 119–120 volts, 200 milliamperes through trunk). Section through right frontal lobe of brain. Stain Weigert-Pál. Photomicrograph (enlargement, 5 \times). Note foci of demyelination in central and convolutional white matter.

due to excessive stimulation of the vagus endings is not known. The pathologic findings suggest the conclusion that the inhibition of the heart had been incomplete and that the tissues have remained viable by a slight amount of circulation maintained by feeble contractions from the inhibited heart for a considerable time, probably several hours. Anoxia and suffocation of the brain tissue was a secondary cause of death.

This may mean that the actual time of death must have been later than frequently assumed in these cases. None of

the structural lesions found in our cases are in themselves incompatible with life; they are not causes of death but only secondary effects of the primary cause of death, indicators of a severe embarrassment and inadequacy of circulation that had existed for some time.

TREATMENT

The treatment is divided into three groups: (1) the treatment of acute shock, (2) the treatment of local injuries at or near the points of contact, and (3) the treatment of central nervous system damage.

1. **The treatment of acute shock** consists mainly in 3 procedures:

(a) Artificial respiration by the prone pressure method should be started as soon as possible and carried out unceasingly and untiringly for eight or twelve hours, until either spontaneous respiration returns or livid patches and rigor mortis appear.

(b) Intracardial injection of atropine and adrenalin.

(c) Lumbar puncture for relief of increased intracranial pressure, repeated if necessary on subsequent days.

Should the occurrence of ventricular fibrillation in human accident cases be confirmed, the intracardial injection of calcium chloride preceded by injection of potassium chloride (Hooker) should be considered as therapeutic aid. It has thus far been carried out only in dogs. The exact procedure is: injection of 13 cc. (per kilogram of body weight) of a potassium chloride solution (0.5 per cent potassium chloride in 0.9 per cent sodium chloride to which 0.25 mgm. of herapin per cubic centimeter were added), followed one minute later by 10 cc. (per kilogram of body weight) of a calcium chloride solution (0.023 per cent calcium chloride in 0.9 per cent sodium chloride); the injection should then be stopped momentarily to introduce 1 cc. of 1:1000 adrenalin chloride into the cannula; and this should then be followed by a further injection of 15 cc. (per kilogram of body weight) of the calcium chloride solution.

Electric countershock through the heart region, for the treatment of ventricular fibrillation, has thus far been used successfully only in fowl (Abildgaard) and sheep (Ferris, Spence, King and Williams). The latter authors recommend an alternating current of 60 cycles, 3000 volts, 26 amperes of 0.1 second duration.

2. **The treatment of local injuries at or near the points of contact** should be started after respiration and circulation have been restored. The burns should be treated like any

others, for example by spraying with gentian violet or by tannic acid dressings. The specific electric skin necroses should be treated by lanolin or petrolatum dressings. Deeper lesions of the subcutaneous tissues, the muscles, and the bone, including those of the skull, should be treated conservatively, at least up to four weeks after the injury. The treatment should consist only in protection from secondary infection by application of sterile dressings, which may be either dry, wet, or greasy. If properly protected, the necrotic areas in electrical lesions do not become infected and, therefore, there is no indication for removal of the apparently necrotic tissue. Metallic impregnation may also give a false appearance of necrosis. In many cases, the lesions heal surprisingly well, while in other cases, in which widespread necrosis, sometimes of an entire extremity, occurs ultimately, the extent of the damage cannot be predicted until several weeks have passed after the injury. The only exception which necessitates radical treatment is in case of profuse hemorrhage: ligation of vessels should then be done at some distance from the lesion, since vessels in the necrotic area are usually brittle and friable. Plastic repair should not be attempted until several months after the injury.

3. The treatment of central nervous system damage is not different from that of similar conditions of other etiology. In the acute encephalomyelitic syndrome with increased intracranial pressure repeated lumbar punctures are indicated, such as carried out in our Case I. In delirium and psychomotor excitement, supervision and sedation are necessary. Paralysis of the bladder with retention of urine (cord bladder) requires treatment by tidal drainage. Paralyzed or paretic limbs (flaccid or spastic paralyses) should be protected from deformity by splints; later they should be treated by physiotherapy, especially massage, motion, galvanic and later faradic stimulation, and radiant heat. The desensitized trunk or desensitized extremities should be protected from decubital ulcers by meticulous care of the skin, proper bedding, and frequent change of position. Parkinsonian tremor and rigidity may be treated by drugs of the atropine series, as in parkinsonian syndromes of other etiology.

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THE MIGRAINE SYNDROME

WITH the exception of such vague entities as "intestinal gripe," "eye-strain," and "sciatica" there is probably no more misused term in medicine than that of migraine. Because its diagnostic criteria vary so greatly, the many publications dealing with its cause and treatment are difficult to evaluate. For this reason I shall enumerate the various symptoms of migraine and indicate the relative diagnostic importance of each.

In the first place, migraine is not a disease but a syndrome. It consists of recurrent severe headaches which are usually attended by nausea and vomiting, and frequently, by visual symptoms. The syndrome occurs against a background of well-being, but the family history is usually suggestive of an hereditary predisposition.

Considering the symptoms in more detail, they are, in order of diagnostic importance, as follows:

1. Recurrent headache, preferably but not necessarily hemicranial. It may be alternating, bilateral or even generalized. However, it must be recurrent. A single exception is the occurrence in an occasional patient of a daily headache for prolonged periods, the so-called "migraine status." However, the presence of a daily headache should always make one suspicious of some new pathologic process which has either been superimposed upon the previous condition or represents the development of permanent changes in the nervous system. (In abdominal migraine, the headache may disappear entirely, leaving only the gastric symptoms.)

2. Visual disturbances associated with the headache are of great value in diagnosis. Classically, these are scintillating scotoma often occurring against an hemianoptic field. More

frequently they consist of blurring, lights, or dancing spots. Pain in the eye, lacrimation, and photophobia are frequent.

3. Gastro-intestinal symptoms, usually nausea and vomiting, are very frequently observed and abdominal pains may occur. In abdominal migraine, the gastro-intestinal symptoms occur without headache. However, the diagnosis of abdominal migraine is dependent on a family history of migraine and also on a history of the earlier association of headaches and gastro-intestinal symptoms.

4. The family history usually reveals the presence of migraine, epilepsy, or allergy in the patient's immediate family.

If these criteria are used, the diagnosis may be regarded as definite when all four are present. The symptoms may then be grouped in order of diagnostic significance as follows: (1, 2, 3, or 4), (1, 2), (1, 3, 4), (1, 4) and finally and least likely (1, 3). As many other conditions may for a time simulate migraine, the diagnosis should always be one of exclusion. One should consider especially the possibility of brain tumor, cardiovascular and cardiorenal disease. Having excluded these and other possibilities and arrived at a diagnosis of migraine, it is then the physician's duty to ascertain, if possible, what is the underlying pathology of the particular case at hand. There should, therefore, be a thorough history and general examination, with emphasis on nervous, endocrine, allergic, psychic and gastro-intestinal factors.

Competent observers have considered the migraine syndrome to be due to ocular, colonic, hepatic, gastric or duodenal disease, psychic maladjustment, various endocrine disorders, cervical tension, autonomic imbalance, and various other causes. Many an observer has been able to collect a series of cases to favor his particular theory. It would appear, however, that like the blind men and the elephant, each had seen the problem only from his own particular point of view.

Observation of a large series of *unselected* cases suggests that the syndrome as a whole has a multiple pathogenesis and that it may be subdivided into various types in which one or another pathogenesis is predominant.¹ In other words, in a large enough series of cases subjected to thorough examination, it will be seen that a certain percentage is primarily allergic, another ocular, etc.

In addition, each individual case, although falling into one or another group, usually is itself composed of several causes, some pathogenic, some contributory.

Thus the treatment of each case must vary considerably according to its particular pathogenesis. No hard and fast rule can possibly be set for the entire group. The prevention of attacks will in one case be accomplished through endocrine, in another through allergic, and in others through other methods. Unfortunately, it is the *prevention* of attacks which causes the physician the greatest distress. Within the past few years we have been able to *terminate* or *abort* migraine headaches regardless of their presumed etiology.² Even such periodic relief has been a boon to physician and patient.

Injection of ergotamine tartrate has terminated or aborted the migraine attack in 90 per cent of over 300 unselected cases presenting the migraine syndrome. Ergotamine is effective in only 10 per cent of nonmigraine headaches.³ Injection of the more recently isolated alkaloid, ergonovine, is completely effective in less than 40 per cent of migraine cases.⁴ It would seem, therefore, that some constituent of ergotamine is specific in relieving migraine headache regardless of the ultimate mechanism of the pain. As the headache is the symptom invariably present in the syndrome, and as ergotamine appears to be specific for its relief, it may be presumed that there is in all cases of migraine a common mechanism productive of the headache. Therefore, study of the action of ergotamine might be expected to reveal the mechanism of the migraine headache.

Headache is an entirely subjective phenomenon. When a patient states that he has a headache, there is no sure way by which the physician may determine whether his pain is organic or hysterical, or indeed whether he has any pain whatsoever. The experienced physician may form an *opinion* with regard to the presence and severity of the patient's complaint, but in the final analysis he must rely upon the patient's statement. For this reason, observations in human beings are unusually complicated and animal experiments are impossible.

We do not yet know the final mechanism which produces any type of headache. However, recent observations by Pickering, Wolff, Clarke,⁵ and others on the headache which

follows the intravenous administration of histamine have given us a good deal of understanding of this particular type of headache.

The headache produced by histamine is due to stimulation of the periarterial plexus surrounding the branches of the middle meningeal and temporal arteries. This stimulation is produced by the arterial pulse acting through an atonic vessel wall which has been relaxed and dilated by histamine.

Wolff and his associates⁶ have shown that ergotamine acts as a vasoconstrictor on the branches of the external carotid arteries (middle meningeal, temporal, etc.). They have also shown that this constriction is synchronous with relief of the migraine headache. The effect of the drug upon the internal carotid arteries is variable and unrelated to the relief afforded. Ligation of either the middle meningeal or the temporal artery has afforded permanent relief from migraine attacks in the few cases in which it has so far been performed.^{6, 7, 8} It is, therefore, probable that the headache of migraine is produced by hypotonic arterial dilation of the branches of the external carotid arteries similar to the dilatation which follows intravenous injection of histamine. The effect of histamine is presumably many times greater than that which occurs during a migraine headache, and ergotamine is not capable of producing enough constriction of these arteries in a "histamine headache" to relieve the pain.

As yet, we have no information concerning the mechanism which may cause such a dilation in migraine. Quite probably different mechanisms are present in the different types of migraine, each of which results in the vasodilation described.

As stated, treatment of the individual attack has been found most effective by means of ergotamine tartrate (gynergen). Treatment should be instituted as early as possible for each attack, preferably during the premonitory symptoms. Emphatically, the use of this drug exerts no prophylactic or preventive effect. Results are most rapid and most effective by the parenteral administration of 0.25 to 0.5 mg., the effect being most rapid after intravenous injection, in which case 0.25 mg. should always be used as an initial trial dose. The subcutaneous and intramuscular routes are only slightly less effective. If parenteral administration is successful, oral ad-

ministration should always be tried. This consists of the administration of 5 mg. by mouth followed by 2 mg. per hour, if necessary, until a total of 11 mg. has been given. The tablets may be utilized sublingually, using slightly smaller doses. If the desired result is not obtained by oral medication, recourse must be had to the parenteral route. Not more than 0.5 mg. should be given at any one injection, nor more than 11 mg. by mouth in twenty-four hours. So far, in my experience, as many as two injections (1 mg.) or 20 mg. by mouth may be given each week for long periods of time without untoward results.⁹ Patients having less obstinate attacks may obtain relief from ergonovine taken in the same manner but in amounts half as large.

The use of the drug is contraindicated in coronary, obliterative vascular, or hepatic disease, acute infection and possible hypovitaminosis. The accidents reported in the literature as following the use of ergotamine have been due in all cases to a disregard of the above precautions.

The use of the drug may and usually does produce unpleasant symptoms, which should, however, not alarm the patient or physician. These are in order of frequency: nausea and vomiting, numbness and tingling of the extremities, muscle pains, fatigue, and substernal oppression. The gastric symptoms may be ameliorated by simultaneous administration of atropine sulfate, $\frac{1}{120}$ grain; the pains and paresthesias, by massage or exercise.

The use of calcium alone may decrease the frequency of attacks. Psychologic readjustment is always helpful but rarely curative. Recourse to blood vessel operations may be recommended in the severe or localized types. Other treatments aiming at the prevention of attacks must be based upon determination of the predominant pathology. Excellent results have been reported by allergists, gastro-enterologists, and endocrinologists. It cannot, however, be too strongly emphasized that each patient presents a problem varying in many respects from every other patient and preventive treatment must therefore be conducted upon an individual basis.

Oliver Wendell Holmes once said, "If I wished to show a student the difficulties of getting at truth from medical experience, I would give him the history of epilepsy to read." I

should like to add that if I wished to show a student the difficulties of medical practice I should give him a headache to treat.

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DIAGNOSIS AND TREATMENT OF MÉNIÈRE'S DISEASE

THE symptom-complex of Ménière's disease, a condition first described in 1861, occurs in medicine as a not too infrequent problem for diagnosis and treatment. No additions have been made to the cardinal symptoms as first described, consisting of the sudden occurrence of violent attacks of vertigo with associated nausea and vomiting. Deafness and tinnitus in one ear may precede or follow the attacks. The attacks are so suddenly severe that patients are "struck down," and walking without aid is usually impossible. This aspect of the disease is a potent factor in differentiating it from episodes of mere lightheadedness and of toxic vertigo.

The pathologic basis for the disease was described originally as a hemorrhagic exudation into the labyrinth. At the present time there is great doubt as to the etiology of the condition, there being insufficient basis for conclusively attributing the condition to a change in any part of the auditory tract. The two most recent etiologic concepts, although quite different in their focus point, attribute Ménière's syndrome to abnormal structural changes adjacent to the eighth nerve, causing irritative pressure on one hand, or a local tissue affinity or sensitivity to sodium on the other. The frequency with which unilateral obstruction of the eustachian tube has been emphasized as the cause of this disease may be based upon incorrect diagnoses. Vacuum states in the inner ear from blocked eustachian tubes may produce ear noises and mild vertigo but not true Ménière's symptomatology. When a diagnosis of Ménière's disease has been made it is implied that a careful otologic examination has excluded all acute or chronic middle or inner ear diseases or involvement of the eustachian

tube. It also implies that a careful neurologic examination, including a roentgenologic examination of the skull, has eliminated intracranial disease, either inflammatory, vascular or tumorous.

The present-day approach to the satisfactory alleviation of the symptoms of Ménière's disease may be either medical or surgical.

In 1930 Muck¹ reported good results in five patients treated by administration of a strict, meatless diet. Dedering,² in 1931, reported that water retention took place in patients with Ménière's disease, as evidenced by the presence of oliguria and subcutaneous edema. Measures aimed at the prevention of water storage, such as a reduced water intake, together with massage, seemed beneficial. This observation played a part in the evolvement of the Furstenberg treatment. Öhnsell,³ in 1931, reported improvement in 4 cases after giving vitamin C. He deduced a relationship of Ménière's syndrome to scurvy. Apparently he overlooked the diuretic effect of vitamin C. Koch and Rothman⁴ (1933) used a diet high in fat, with restricted salt and meat intake, with success. Allergy as a basis for Ménière's disease was expressed by Yandell⁵ in a case report in which he established a relationship with orris root sensitization. Morgan and Baumgartner⁶ (1934) obtained an excellent result in Ménière's disease following cervical ganglionectomy. Foldes⁷ (1935) compared Ménière's disease to such conditions as epilepsy, eclampsia, migraine, bronchial asthma and gout, which he attributed to temporary retention of water and mineral. The attacks ceased when the retained liquids disappeared from the respective organ. His treatment consisted of antiretentional measures, low protein diet, and quinine sulfate.

The medical management giving most promise at the present time is that described by Furstenberg,⁸ which consists of administration of a sodium-poor diet, the avoidance of salt, and the administration of 6 to 8 Gm. of ammonium chloride a day for three days with two days off. This régime can be continued for months without apparent ill effects. It is essential at the time of submitting this régime, that the patient have as thorough an understanding of the disease and its treatment as an individual who successfully treats his severe

diabetes. In many instances success or failure has depended upon time spent in training the patient as to the why and wherefore of the treatment. Brown⁹ (1937) has verified the benefits of this plan of treatment.

If after meticulously following such a régime, relief is not obtained and the symptoms remain severe enough to prevent work, the patient should be referred to the neurosurgeon for treatment. The surgical maneuver consists of sectioning the entire eighth nerve if deafness is present; if not, the part of the eighth nerve to the vestibular portion is severed, leaving the fibers to the cochlea intact. The surgical approach will not be given in detail. This information will be found in the writings of Dandy.

As this paper is intended to emphasize the medical management of this disease, suffice it to say that at the Lahey Clinic up to June, 1937, 8 patients were operated on for Ménière's disease by section of the eighth nerve. No mortality occurred. Of these, 7 obtained complete alleviation of their attacks of vertigo. The explanation for failure to obtain relief in 1 case was attributed to incorrect diagnosis or too long-standing disease.

SURVEY OF PATIENTS TREATED MEDICALLY

Eighteen patients were placed on medical management, consisting of the plan of Furstenberg. Eight of the group were men and 11, women. The average age was forty-nine years, with the range of ages from twenty-nine to sixty years; 9 patients were between fifty and sixty years of age. All of these patients met the outstanding requirement for a diagnosis of Ménière's disease, that is, recurring attacks of severe vertigo usually with associated nausea and vomiting and associated ear symptoms.

Duration of symptoms varied from one month to twelve years. In 4 cases it was less than six months, in 2 cases the duration was not stated, and in the remaining 12 cases the average was slightly less than six years.

The attacks occurred at variable intervals from once in six months to as frequently as three to four times in one week. Although the onset of the attack is characteristically precipitous, some patients have had a short period of warning,

taking the form of a feeling of uncertainty or unsteadiness. The duration of these attacks of upheaval of equilibrium varied from a few minutes to as long as four days. The usual length of time was several hours, with a period of profound prostration lasting several days, usually in direct relation to the duration of the attack. Eleven of the patients had severe nausea and vomiting, the remaining 8 only mild gastric symptoms.

Thirteen patients had symptoms referable to one or both ears. These symptoms were chiefly buzzing, roaring and deafness. They preceded or had their onset at the time of the first attacks of dizziness. The buzzing, which at first is intermittent, frequently became permanent. Once the deafness started it usually progressed slowly until complete loss of hearing occurred.

The examination of the ears did not reveal objective changes. Of 15 cases in which careful hearing tests were made, 12 patients were found to have varying degrees of deafness of the nerve deafness type. In many patients the deafness was bilateral by test, not of the same degree, although the patient was aware of the change only in one ear.

The physical examination was surprisingly void of systemic disease. The occurrence of vascular disease with its various manifestations was not noteworthy. Hypertension was noted in only 1 patient. These findings seem to take Ménière's syndrome out of the realm of degenerative disease and make it a metabolic or functional disease. No changes of significance were recorded in the routine laboratory studies, which included erythrocyte and leukocyte counts, differential blood count, urine analysis and test for syphilis.

RESULTS OF MEDICAL TREATMENT

The régime of Furstenberg was used in treating these 18 patients. It is to be noted that these were out-patients and naturally treatment could not be controlled as well as with Furstenberg's patients who were hospitalized for thirty days under careful medical observation. Twelve of the 18 patients obtained complete relief of the acute attacks. Of these, 2 patients still had annoying ear noises. The duration of the disease varied from one month to twelve years. the average

being six years. The period of observation after starting the diet was as long as fourteen months and as brief as one month, the average being only five months. Two of the patients had foci removed: 1, tonsils, and the other abscessed teeth. Of considerable interest was the fact that 1 patient had a recurrence when the diet was not adhered to and another could precipitate an attack by eating salted peanuts. One patient was so systemically benefited that there was a gain of 8 pounds.

Two patients obtained only partial relief after being on the régime one month and one year, respectively. Four patients were not relieved by the program of treatment. It seems significant that 12 patients were so distinctly aided, this overshadowing the 6 who were partially or not benefited, since mistakes or lack of faithfulness in home management are likely to be manifold. Many patients have continued to carry out the treatment, thus evidencing their utter satisfaction with this form of management. This fact speaks well for this type of therapy.

SUMMARY

The diagnosis of Ménière's syndrome is based on the presence of certain cardinal symptoms occurring in patients in whom obvious middle and internal ear pathology has been excluded. Although the pathology of this condition still remains obscure, benefit can be obtained in most cases by the use of the low sodium diet régime as outlined by Furstenberg. Twelve patients out of 18 here reported obtained complete relief of their incapacitating symptoms. If failure is met under medical measures surgery offers great possibility for relief.

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THE DIFFERENTIAL DIAGNOSIS OF PULMONARY TUBERCULOSIS

MUCH progress has been made in the certainty with which pulmonary tuberculosis can be recognized clinically. This is due to developments in the field of roentgenology. Extensive application of the x-ray in chest conditions has led to an appreciation of its importance in the detection of early tuberculosis and made it apparent that there are serious limitations in the reliance alone on the history and physical examination in the diagnosis of the disease.

In the diagnosis of pulmonary tuberculosis the following considerations are important from the point of view of the history:

Exposure to tuberculosis in the family or other opportunity for contagion has an important bearing on the diagnosis in doubtful cases.

A history of hemoptysis out of a clear sky, or when cough and scanty expectoration alone cloud it, is especially suggestive of pulmonary tuberculosis, and the suspicion of tuberculosis holds as well when the bleeding occurs during a mild acute respiratory infection, after exertion, moderate injury or without any apparent cause. Exceptions to a tuberculous origin in this group are uncommon. They have increased with the diminishing frequency of tuberculosis and unabated incidence of other causes. The exceptions are for the most part due to malignant disease. This is usually of bronchial and at times of pulmonary origin. In rare instances, hemoptysis is an initial symptom of bronchiectasis, the rupture of tuberculous or anthracotic glands into the air passages or syphilis of the trachea and bronchi. In certain regions echinococcus disease or *Distoma ringeri* may be a cause.

Equal in importance to hemoptysis out of a clear sky in suggesting tuberculosis is primary pleurisy with or without an effusion. Here also malignant disease is the most common cause of confusion. A malignant process primary in the bronchi or lung may be unattended with other significant symptoms than those arising from extension of the growth to the pleura. In rare instances a new growth is primary in the pleura. Pleural effusion when it occurs as a consequence of malignant disease is usually bloody. Examination of the sediment after fixation, section and staining may permit a diagnosis. Latent thrombophlebitis, pulmonary embolism and infarction may also be the cause of an apparently primary pleurisy, if such other symptoms as dyspnea and pain in the side are absent. Bloody expectoration after operation, delivery or trauma should suggest the possibility of infarction.

The evolution and grouping of symptoms are important in the differentiation of tuberculous and nontuberculous lesions. In the discussion of the clinical aspects primary pulmonary tuberculosis may first be considered.

Primary, or first infection tuberculosis, is most commonly observed in children, but may also occur in adults. The disease, unlike that arising as a secondary infection, is not commonly confined to the apical or subapical region, but may be at any part of the lung as diffuse or nodular lesions and is associated with tracheobronchial glandular enlargement. Tubercle bacilli can usually be demonstrated in the sputum or the stomach contents. The onset is insidious. Cough with or without expectoration and fever are usually present. The tuberculin test is positive and leukocytosis is absent. Resolution is slow, leaving calcified areas and fibrosis in the lung and calcified tracheobronchial lymph glands.

The principal difficulty in the diagnosis of first infection pulmonary tuberculosis is its distinction from acute bronchopneumonia and lobar pneumonia. In these conditions, however, the onset is likely to be stormy. The tuberculin test in children may be negative. Tubercle bacilli are absent in the sputum and gastric contents, and leukocytosis is usually present. In favorable cases, resolution is relatively rapid in nontuberculous pneumonia. Calcification does not take place in the involved regions.

Of secondary infections with the tubercle bacillus that form known as acute pneumonic phthisis, or acute tuberculous pneumonia, is fortunately rare. Its differentiation from acute pneumococcus pneumonia is of special importance because of the desirability of early specific antiserum therapy in certain types of pneumococcus pneumonia. There are in general significant differences in the two types of infection, but it is at times difficult to distinguish the one from the other early in the course of the illness. In contrast to acute tuberculous pneumonia the pneumococcus infections usually occur in previously healthy individuals. The onset is commonly more explosive with shaking chill, rapid elevation of temperature, cough with tenacious, rusty sputum and pain in the chest. This typical complex of initial symptoms is more common with pneumonia due to Type I or II pneumococcus than other types, and the finding of these types in the sputum speaks for pneumococcus pneumonia. The initial complex of symptoms is less often typical with pneumonia due to types of pneumococci above Type III, and the differentiation from tuberculosis may in consequence present greater difficulty. The onset of acute tuberculous pneumonia is, however, less likely to be explosive. Chill and pain are less common. Rusty sputum may occur, but greenish expectoration is more often observed. Frank hemoptysis may be an initial symptom. Pallor rather than cyanosis, greater irregularity in the temperature fluctuations, remittent or intermittent fever, failure to become afebrile at the expected time, absence of leukocytosis and physical and x-ray evidence of apical or subapical involvement in addition to consolidation elsewhere are suggestive features. In all cases of pneumonia the sputum should be investigated, both for tubercle bacilli and pneumococci. If pneumococci are present, their type should be determined. With acute tuberculous pneumonia, tubercle bacilli are usually present in the expectoration.

Failure to make an early diagnosis of the common or chronic ulcerative form of pulmonary tuberculosis is largely due to a long, latent interval during which there are no significant symptoms or physical signs. During this period the disease can be recognized only by x-ray examination. A considerable proportion of patients in the early stages of the dis-

ease may be expected in the investigation of family and other contacts.

As the pulmonary tuberculosis progresses beyond the latent period, a fairly uniform evolution and grouping of symptoms may be expected. The earliest symptom of pulmonary tuberculosis which has passed beyond the symptomless stage is likely to be cough. The cough is at first dry and after a variable period productive of at first scanty and mucoid and later mucopurulent sputum. Such other symptoms as fever, night-sweats, malaise, anorexia, loss of weight and strength and elevated pulse may be present in actively progressing lesions. Dyspnea is usually a late and relatively insignificant manifestation. Pain is often absent. When present it is usually of a dull aching character.

Owing to the variability of the symptoms, almost any of the more chronic types of pulmonary disturbances may simulate tuberculosis, but the manifestations may depart sufficiently in the order of their appearance from those with tuberculosis to be suggestive. Space does not permit full discussion of the matter, but the following may be taken as examples.

One of the most common sources of error is the confusion of bronchial tumor with tuberculosis. The symptoms may be much the same in the two conditions, with cough at first, with dry and later with mucoid and mucopurulent sputum, not infrequently blood-streaked or frankly bloody. At times, with bronchial tumor hemoptysis is an initial symptom and recurs at varying periods with complete freedom from significant intervening symptoms. In cases in which there is obstruction of a large bronchus, dyspnea may be an early symptom and wheezing may be noted especially when lying on the affected side. Elevation of temperature not infrequently occurs from the trapping of infection beyond the bronchial obstruction. Night-sweats are usually absent and leukocytosis is likely to be present. x-Ray examination fails to show mottled increase of density in the subapical region.

It should be appreciated that with bronchial tumor until bronchial obstruction occurs, physical and x-ray examination may be negative. For the determination of the cause of bronchial obstruction, further investigation must be considered.

and in selected cases resort must be made to bronchoscopic examination and removal of tissue for biopsy.

Bronchiectasis may also be confused with tuberculosis, especially in cases with hemoptysis. Profuse bleeding is not uncommon, but is rarely an initial symptom. In the distinction of bronchiectasis from tuberculosis, an offensive odor to the sputum, repeated failure to demonstrate tubercle bacilli in the sputum, x -ray evidence of dilated bronchi at the bases and absence of subapical involvement are important.

In these two conditions, bronchial tumor and bronchiectasis, the confusion with tuberculosis is most likely to occur in cases in which the investigation falls short of completion by the omission of x -ray examination.

Physical signs are far less valuable than the x -ray in the recognition of pulmonary tuberculosis and its distinction from other diseases. Inevitable failures in the detection of pulmonary lesions and the interpretation of their nature are not uncommon in spite of the greatest care and experience in the performance of physical examination when reliance is placed on this method alone.

Physical signs may be absent with early active or with indolent and deep-seated tuberculous lesions. In cases with typical symptoms, the persistent presence of moist râles at the apical or subapical regions and negative findings elsewhere are suggestive of pulmonary tuberculosis, but may be due to other causes and cannot be accorded equal importance in diagnosis to the finding of x -ray densities similarly placed and consistent in appearance with pulmonary tuberculosis.

Much reliance can be placed on physical signs in the detection of large areas of consolidation and considerable amounts of pleural fluid or air. Small areas of consolidation, however, may not be detectable by physical examination, and are especially likely to be missed when deep-seated. Tumors, cysts and deep-seated abscesses may give no significant physical signs. Small accumulations of air in the pleural sac are incapable of detection as such by physical signs and cannot be distinguished from obstruction emphysema without x -ray examination.

In the diagnosis of obstruction atelectasis such physical signs as dullness, diminished or absent breathing, without bron-

chial breathing, diminished voice without egophony, and diminished tactile fremitus are significant, but are present also with such other conditions as tumor, cyst, unevacuated abscess and the elevated diaphragm. Here also the x-ray may be indispensable in differential diagnosis. So far as atelectasis is concerned, though the x-ray is important in establishing its presence, it cannot be expected alone to furnish evidence sufficient to determine whether the afferent bronchus is open or closed. Physical signs may here be of great assistance provided the collapsed area is of sufficient size. In the presence, for example, of collapse involving one of the four larger lobes, bronchial breathing, increase of voice, whisper and tactile fremitus may be taken to indicate the presence of an open bronchus. When the middle lobe is involved, however, owing to its small size the patency of the afferent bronchus may be determined only by bronchoscopic examination. In general it may be said that physical signs are of great assistance in cases with atelectasis of one of the large lobes of the lung in the decision regarding bronchoscopy or its repetition.

The differential diagnosis may be discussed in connection with such special investigations as sputum examination, the white count and tuberculin.

The desirability of examination of the sputum for tubercle bacilli in all pulmonary infections should be more generally appreciated. The odor of the sputum is of some diagnostic value. It is usually odorless with uncomplicated pulmonary tuberculosis, stale or musty in about one half of the cases of bronchiectasis, and foul with few exceptions with lung abscess.

The usual absence of leukocytosis with uncomplicated pulmonary tuberculosis makes the white count of importance in the distinction between tuberculous and nontuberculous infections.

Tuberculin is of value in differential diagnosis in excluding tuberculosis in difficult cases. In cases in which the intracutaneous tuberculin test is negative with increasing doses up to and including 1 mg., tuberculosis can with rare exceptions be excluded.

The diagnostic importance of positive tuberculin tests diminishes as age advances, owing to the greater incidence of a reaction to tuberculin in the older age groups. Positive tub-

culin tests may be taken to mean that infection with the tubercle bacillus is present somewhere in the body and not necessarily in the lung. Such tests can be interpreted only by taking into consideration other aspects of the case and especially the x-ray examination of the lungs.

The x-ray is indispensable in the recognition of pulmonary tuberculosis at an early stage of the disease. Fine or coarse mottled increase of density above the anterior portion of the third rib is seldom due to other causes. In cases in which the clinical aspects and the x-ray findings are both consistent with pulmonary tuberculosis the diagnosis can be made with little chance of error. In doubtful cases, repetition of the x-ray at frequent intervals is of assistance in the decision, as the shadows due to tuberculosis change only slowly or not at all and nontuberculous areas may disappear.

While it may be impossible to differentiate bronchial tumor from pulmonary tuberculosis by the history and physical signs, the x-ray findings furnish important evidence for or against tuberculosis and ordinarily go far toward establishing the presence of bronchostenosis. Inasmuch, however, as pulmonary tuberculosis may be complicated by bronchial obstruction, bronchoscopy may be necessary to establish the nature of the obstruction.

It is important to appreciate that in selected cases, more than the usual anterior-posterior x-ray view is desirable. It is in general well to keep in mind the possibility of bronchial obstruction in difficult chest cases and take the precaution of having an x-ray examination not only in the anterior-posterior, but also in the lateral view and at the end of full inspiration and at the end of full expiration.

The absence of fine or coarse mottled increase of density in the x-ray films above the anterior portion of the third rib is to be regarded as important evidence against the adult type of tuberculosis. Though complete reliance cannot be placed on such negative evidence in excluding the disease, nevertheless the chance is small that pulmonary tuberculosis as a secondary infection is present under these circumstances.

With valvular bronchial obstruction, the resulting overdistention of the lung may be apparent in increased radiance of the affected region, depression and partial fixation of the

diaphragm on the side of the lesion, increased excursion of the diaphragm on the opposite side and displacement of the heart and mediastinum toward this side. Though physical signs may be the same with pneumothorax and with obstruction emphysema, the two conditions are readily differentiated by x-ray examination.

With obstruction atelectasis involving one lobe, the x-ray findings comprise changes due to the collapse itself and to disturbances in neighboring regions. With respect to the involved region, an area of lobar collapse is seen in the x-ray as a dense homogeneous shadow with sharply defined borders. The site and contour of the collapsed area, together with such secondary changes as displacement and inspiratory dislocation of the heart and mediastinum toward the affected side, narrowing of the lung field and intercostal spaces, downward inclination of the ribs and elevation and diminished motion of the diaphragm present an appearance not likely to be confused with other conditions.

As already noted, in the differentiation of pulmonary tuberculosis from bronchiectasis, x-ray evidence of dilated bronchi at the bases and absence of subapical involvement are of importance. It is usually impossible definitely to establish the presence of dilated bronchi by x-ray, however, without resort to the instillation of lipiodol into the involved region after the evacuation of purulent material. Cylindrical dilated bronchi then appear as finger-like processes of larger caliber than normal bronchi in the involved region. Nontuberculous bronchiectasis is prevailingly basal and without subapical changes characteristic of tuberculosis.

The differentiation of tuberculosis from lung abscess is not ordinarily difficult. With abscess there is often the history of onset following operation on the upper respiratory tract. The sputum is almost always of foul odor. On x-ray examination lung abscess is likely to show as a single area of increased density at the periphery of the affected lobe, with central radiance and fluid level. The sputum is rarely foul with tuberculosis, the subapical region is likely to be involved and cavities, if present, are likely to be in this region. There are rare instances, however, of tuberculous cavities elsewhere than at the apices in cases without x-ray changes suggestive of the disease.

at the apical or subapical regions. Absence of foul odor to the sputum in such cases should raise the suspicion of tuberculosis and this suspicion may be confirmed by the finding of tubercle bacilli in the sputum.

In the differential diagnosis of pulmonary tuberculosis from the conditions with which it may be confused, the examinations already discussed will ordinarily suffice. In chronic cases in which the evidences suggest the presence of broncho-stenosis it is desirable in selected cases to pursue the investigation further by resort to bronchoscopy without which it may be impossible to determine the nature of the obstruction.

CLINIC OF DRS. ELLIOTT P. JOSLIN, HOWARD F. ROOT, PRISCILLA WHITE, ALEXANDER MARBLE, AND ALLEN P. JOSLIN

FROM THE GEORGE F. BAKER CLINIC, NEW ENGLAND
 DEACONESS HOSPITAL

PROTAMINE (ZINC) INSULIN

- I. INTRODUCTION.
- II. COMMONPLACE HYPOGLYCEMIC REACTIONS AND THEIR PREVENTION.
- III. LOCAL SKIN RESPONSES.
- IV. EVALUATION WITH CHILDREN AS AN INDEX.
- V. USE IN SURGERY, PERNICIOUS ANEMIA, AND HYPERTHYROIDISM.

I. Introduction.—As an introduction to the treatment of diabetics with protamine zinc insulin we present the accompanying table (Table 1). This table shows the treatment of

TABLE 1
 DIABETICS UNDER OBSERVATION AT GEORGE F. BAKER CLINIC IN
 NEW ENGLAND DEACONESS HOSPITAL AND PRENDERGAST PREVENTORIUM
 January 31, 1938

Case.	Sex.	Age, years.	Duration of diabetes, years.	Days in hospital.	Insulin. Reg. Protamine.	Complications.
1	M.	27 2	12.0	127	10 [54]	Plastic on ureteral anomaly.
2	F	58 9	5.6	69	[10]	Amputation toes.
3	M.	59.1	5.2	62	None.	Amputation toe.
4	F	63 7	2.1	52	[12]	Amputation toe.
5	F.	72 2	18.6	51	None.	Lymphangitis. Amputation toe.
6	M.	68.1	6.5	51	None.	Osteomyelitis toe.
7	F	58 5	3 1	44	[10]	Carbuncle neck. Syphilis.
8	F	59 3	13.1	39	[18]	Amputation lower leg.
9	F	64.7	20.1	33	6 [24]	Amputation thigh.
10	F	43 3	3 3	34	[44]	Gallstones. Cholecystectomy.
11	F	66.8	4 1	32	[32]	Amputation toe.
12	F.	53 5	13.1	29	None.	Neuritis.
13	M.	66 4	10.1	23	[6]	Hyperthyroidism, thyroidectomy.
14	F	57.0	2 1	23	[40]	Cellulitis lower leg.

TABLE 1—Continued

Case.	Sex.	Age, years.	Duration of diabetes, years.	Days in hospital.	Insulin. Reg.	Protamine.	Complications.
15	M.	59.8	15.6	20		8	Coronary occlusion. Gallstones.
16	F.	78.0	2.6	20		12	Hypertrophic arthritis.
17	M.	45.9	1.3	19	None.		Urethral stricture.
18	M.	64.1	2.0	17	None.		Evulsion toenail.
19	F.	27.9	9.1	17	18	36	
20	F.	60.9	9.4	17		12	Cholecystitis.
21	F.	54.4	0.9	15		16	Amputation toe.
22	F.	18.3	15.0	13	16	48	Appendectomy.
23	F.	58.8	1.1	12		32	Amputation finger.
24	M.	25.6	10.6	11	10	44	Appendectomy.
25	F.	62.9	1.5	11		20	Amputation thigh.
26	F.	66.3	1.8	10		20	Colitis.
27	M.	60.0	7.0	9		20	Coronary occlusion
28	F.	61.3	0.2	9	16	38	Chronic cystitis.
29	M.	72.3	9.9	9		12	Amputation thigh.
30	M.	65.5	15.0	7		16	
31	F.	57.7	8.5	7	8	40	Osteomyelitis.
32	F.	70.7	11.6	7	6	36	Cystitis. Infection leg.
33	F.	48.6	1.7	7		16	Cancer. Panhysterectomy.
34	F.	59.9	8.0	7	20	20	Goiter adenomatous.
35	F.	52.2	1.7	6	10	30	Felon.
36	M.	19.9	0.2	5		28	
37	F.	50.6	19.6	5		18	Osteomyelitis.
38	F.	13.7	5.6	5	32	52	
39	F.	54.2	0.3	5	12	36	
40	F.	23.3	7.1	5	20	58	Frost-bite toe.
41	M.	47.3	11.6	5	18	44	Diabetic coma.
42	F.	39.9	15.0	5	18	44	
43	F.	13.3	11.6	4	16	44	
44	F.	55.0	10.7	4		6	
45	F.	57.1	22.1	3	48	52	
46	M.	63.4	25.9	3	10	12	
47	M.	68.8	9.2	3	None.		Papilloma bladder.
48	M.	63.9	5.2	3	10	20	Cystitis.
49	F.	22.3	9.9	3	30	80	Neuritis.
50	M.	52.2	6.6	3	16	56	Amputation gallbladder.
51	M.	49.1	1.9	3		16	
52	F.	64.3	7.7	3		20	Infection toe.

TABLE 1—Continued

Case.	Sex.	Age, years.	Duration of diabetes, years.	Days in hospital.	Insulin. Reg. Protam. ine.	Complications.
53	M.	53.1	4.5	2	[10]	
54	F.	55.9	3.6	2	5	Cardiac decompensation.
55	F.	37.1	10.2	2	[34]	Gastric ulcer.
56	M.	14.6	10.0	2	12 [52]	Pneumonia.
57	F.	56.8	0.2	1	None.	Paronychia finger.
58	F.	25.9	6.5	1	None.	
59	M.	43.4	1.6	..	15	
60	M.	62.6	8.9	..	None	Neuritis.
61	F.	56.4	15.5	..	56	Neuritis.
62	F.	12.0	3.0	579	6 [36]	
63	F.	12.8	1.5	485	12 [54]	
64	M.	12.0	5.0	316	6 [52]	
65	M.	8.0	6.0	579	4 [32]	
66	F.	8.6	2.3	518	12 [26]	
67	M.	11.5	10.4	396	[28]	Dwarfism.
68	F.	10.5	9.2	248	18 [70]	Dwarfism.
69	F.	11.6	5.5	18	10 [24]	
70	F.	6.0	2.0	208	[22]	
71	F.	12.9	9.5	25	12 [22]	Pretubercular.
72	F.	7.5	1.4	518	[28]	
73	M.	7.3	1.3	274	[22]	
74	M.	12.0	1.0	244	[28]	Pretubercular.
75	M.	16.6	12.6	883	22 [76]	Dwarfism.

75 diabetic patients, 61 in the New England Deaconess Hospital and 14 in the Prendergast Preventorium on Monday, January 31, 1938. Of the 61 patients at the Deaconess Hospital there were but 3 taking regular insulin and these were patients who had been at the clinic for two days or less. All of the 14 children at the Prendergast Preventorium were treated with protamine insulin but it happened that on this day clinical tests for various purposes were being performed with regular insulin and therefore we have taken the liberty to insert the customary doses of regular and protamine insulin which these 5 children usually employed.

Of the 61 patients at the Deaconess Hospital 10 received no insulin, 21 took combined regular and protamine insulin before breakfast and the remaining 27 protamine insulin alone.

At the Prendergast Preventorium 9 of the 14 patients used regular and protamine insulin and the remaining 5 protamine alone. The average total daily quantity of insulin for the 65 patients receiving it was 38 units. The average quantity of protamine insulin for 31 taking it alone was 20 units and the average division of regular and protamine insulin for those using both varieties before breakfast was 15 units of regular and 42 units of protamine insulin. In all instances protamine insulin was given exclusively before breakfast and this holds for cases in which both regular and protamine insulin were employed. In a very few patients supplementary doses of regular insulin were given later in the day because of various complications.

Our diabetic patients under observation at the Deaconess Hospital and Prendergast Preventorium present a cross section of diabetics generally. Thus, 28 were males and 47 females. The youngest was six and the oldest seventy-eight years. The average age was 43.6 and the mean age was 53.5. The duration of the diabetes varied from a few months to 25.9 years. The average duration was 7.4 years and the mean duration 7.0 years.

The diet of the patients varied considerably. Thus, the carbohydrate ranged between 65 and 249 Gm., the average being 147. The protein varied from 39 to 120 Gm., the average being 69 and the fat from 49 to 130 Gm., the average being 87 Gm. These figures apply to the patients in the Deaconess Hospital proper. The children received more food and the average carbohydrate was 199, protein 83, fat 94 Gm.

Complications were the rule. Thus, there were 30 surgical cases. The overwhelming proportion of these related to lesions of the lower extremities. Five of the number had undergone amputation of the thigh or leg and 8 of one or more fingers or toes. Four were under treatment for osteomyelitis or infections of the feet. There were two cases with a finger involved, one with gangrene and one with osteomyelitis. Hyperthyroidism with operation was represented by one patient and one other patient was under treatment awaiting operation for adenomatous goiter. One patient had a carbuncle, another had been operated upon for cancer of the uterus, two patients were recovering from appendectomies. Three patients had gall-

stones, of whom one had been operated upon. A single patient had plastic operation for an ureteral anomaly. Neuritis, coronary occlusion, hypertrophic arthritis of extreme degree, colitis, cystitis were also represented but it was notable that diabetic coma occurred in but one instance. Although the number of cases in the clinic was larger during January, 1938, than in 1937 there was but one case of diabetic coma in the whole month this year as compared with 3 cases last year. Three of the children presented dwarfism and 2 were pretubercular in character. We are glad to mention these complications in detail because they illustrate the wide usefulness of protamine insulin in our hands just as does the wide range in the age of the patients and the duration of the disease.

We now wish to discuss various aspects of treatment which have arisen with our use of protamine insulin as illustrated by the following clinical cases.

"The change from regular insulin to protamine insulin has been wonderfully helpful to me," said Mr. R. R., 9546, today, January 28, 1938, at his semiannual visit. He is now forty-one years old with diabetes of ten years' duration, living upon carbohydrate 160, protein 80 and fat 110 Gm., and takes 28 units before breakfast. "It makes life so much more comfortable." This is the story we are constantly hearing and another, which we heard today and consider of even greater importance, because it shows the difference in the attitude of the new patients toward insulin is this: "I hope you will not need to take insulin, mother, but of course, if you do, you know the new insulin is injected but once a day." Protamine insulin has "put insulin across" and, as it is the use of insulin which keeps diabetics alive, it is hard to estimate how many more of them will be living five years from now due to this fact. It is worth while to study carefully how to treat diabetics, who live long and come back, as to care for patients with diseases with less prosaic names yet where life is either short or a return unnecessary.

Unhesitatingly, therefore, we recommend the use of protamine insulin. Recently on our entire service at the George F. Baker Clinic there was not a single patient taking regular insulin alone and in order to test the strength of the latter, in special samples submitted for that purpose, we have been com-

pelled deliberately to specify that temporarily a few cases shall not receive the protamine variety. Since the summary of our experience with protamine insulin was published in the Journal of the American Medical Association, August 14, 1937, 109:497, we do not think that any cases who were transferred to protamine insulin have returned permanently to regular insulin.

The fundamental facts to be remembered in the use of protamine insulin are that it acts slowly, that its action is not spent until after about forty-eight hours and that if carbohydrate is not constantly supplied it can behave as "a roaring lion seeking whom he may devour."

II. Commonplace Hypoglycemic Reactions and their Prevention.—Allowing that under enlightened medical surroundings diabetic coma should not exist and that diabetic gangrene usually can be avoided, we have insulin reactions as one of the most annoying, embarrassing and crippling complications of diabetes. To be sure at present they are better understood and more condoned by the laity, but nevertheless the possibility of an insulin reaction interferes with the self-reliance of a diabetic, exposes him to gossip, prevents his participation in many undertakings and actually hinders his securing or holding a job. All of us hoped that protamine insulin would not cause reactions, but it does. They are not more frequent. Mr. T. B., 10435, said this morning he had had but one reaction and that when playing golf at an unusual hour. He felt for his sugar, but the day was so hot it had melted in a sweaty pocket. He was on the outskirts of the course, far from the clubhouse. In despair like Abraham, he "lifted up his eyes and looked, and behold behind him" not "a ram caught in a thicket by his horns" but instead blueberries on a bush, and the hypoglycemia was assuaged.

The characteristic symptoms of reactions due to protamine insulin are headache, nausea, and malaise. These persist for considerable periods of time and often are unrecognized, and the patient thinks he is losing ground. Frequently they cause more complaints than the more acute but temporary hunger, tremor, nervousness, and sweating which signalize the reactions of regular insulin. It is true both groups of symptoms may be present together and also true that although reactions due to protamine insulin, usually come on gradually they may break

out as suddenly as with regular insulin. They are best avoided by matching the protamine insulin with food—3 meals and 3 light lunches—and also by offsetting the blood sugar lowering effect of exercise in a similar manner. So important do we consider reactions and the need for their prevention to be that we shall report the occurrence of these in 3 reliable cases.

Miss M. F., 16185, whose diabetes began in 1931 at the age of fifty-eight, came into the clinic October, 1937, taking carbohydrate 160, protein 65 and fat 75 Gm. with protamine zinc insulin [28] units before breakfast. Her weight undressed was 53 kg. Since the onset of the disease treatment had been excellent. However, the patient was meticulous as to diet, insulin and tests and much annoyed by reactions of any type of severity which would come on at irregular hours but especially in the late afternoon, evening, night or early morning. Diet and total dosage of insulin appeared excellent although at times the total sugar excreted in twenty-four hours did go up to fairly high levels and during eighteen days' period of readjustment, it reached above 50 Gm. on three days although below 20 Gm. on eleven days. She was finally regulated by using regular insulin 10 units in combination with protamine zinc insulin [18] units before breakfast. *Before retiring she appeared to do better with 10 Gm. of carbohydrate in the form of biscuits along with 15 Gm. of cheese than by taking very soluble carbohydrate like orange juice. And in the morning she had her breakfast fruit simultaneously with her doses of insulin.* Often patients have an early cup of coffee. As a result of these simple measures she left the hospital with less fear of insulin and said she felt better than for some years. The whole point of the case was that whereas the patient was on a perfectly good diet and taking a perfectly satisfactory total dosage of insulin when she came, she was unhappy and needed trifling changes in her régime. By being under observation in a hospital, it was relatively easy to bring these about by securing a multitude of urinary and blood sugar tests. The latter were done on capillary blood, drawn from the ear, thus producing less inconvenience than as if by puncture of a vein.

Miss M. Q., 4715, developed diabetes at the age of five years in 1925. Under careful treatment she grew normally, never experienced diabetic coma, but she was much annoyed

by eczema and by symptoms related to a megacolon. She began protamine insulin in February, 1936, and upon it was fairly well controlled, 85 per cent more or less, upon a diet which varied little from carbohydrate 175 Gm., protein 80 Gm., fat 110 Gm. and Reg. I. 18-P. I. [36] units before breakfast. Her weight was 114 pounds naked and height 63½ inches in June, 1936, when sixteen years old.

During July she was in excellent condition and exercising vigorously. On two days of hard climbing in the White Mountains she experienced no inconvenience, protecting herself against reactions by additional food. She was as well as usual on the day following. Following a noon dinner she lay down for a nap and it was during this that she had a prolonged convulsive seizure the beginning of which was not recognized. She was given 0.5 cc. adrenalin and this was repeated twice at 10-minute intervals and again once later to no avail. Consciousness returned only with the giving of glucose intravenously, the previously given rectal glucose presumably having been of little effect.

She and her parents never anticipated that an insulin reaction would occur so long after exercise. It can be explained by the good effects of exercise in a severe diabetic while under the influence of insulin. The persistence of action of the insulin into the second day was not considered and treated by additional carbohydrate, this having been thought only necessary during and immediately following the period of actual exercise. Action of 3 forces, (1) the continued and prolonged effect of protamine insulin in an individual (2) whose blood sugar was lowered to an unusual extent the previous day by exercise, and (3) in consequence of which glycogen reserves had been reduced to such an extent that the customary dose of insulin was excessive.

Case 3, Mr. C. C., 14575, a lawyer, was seventy-five years old when his diabetes began in March, 1936, and when we first saw him in May the urine contained 9.2 per cent sugar and the blood sugar was 0.49 (490 mg.) per cent. He responded well to treatment and his weight which had fallen from 189 pounds dressed to 149 pounds at the first visit was 151 pounds at his recent visit January 25, 1938.

The episode which led his family physician to telephone for

an immediate consultation happened before breakfast September 22, 1937, when his servants, suspecting something unusual, broke open his bathroom door and found him unconscious. Over the telephone we ruled out coma, because his recent health had been excellent, he was conscientious in testing his urine, in dieting and with the administration of insulin. Further, he was known to have been conscious that morning. Therefore, we told the young doctor, who was called in for the emergency, that we thought a consultation was unnecessary and that his patient would recover with adrenalin and intravenous glucose. He was so alert as to use these promptly, as well as a capsule of caffeine sodium benzoate. Recovery was instant, greatly to the reputation of the young doctor, because the patient was a prominent citizen. Now for the cause of the reaction.

When this patient entered the hospital in May, 1936, with as much as 9.2 per cent sugar, we knew his diabetes was of short duration because otherwise he would have been more reduced, were happy in the thought that his metabolism had not been injured by a low carbohydrate high fat diet, realized though old he had a young type of diabetes which would respond well to treatment, although as with children it might be necessary to give considerable quantities of protamine insulin. Therefore, his protamine insulin was gradually increased from 10 units the first afternoon to 20-0-10 the next day and thereafter to protamine insulin once a day, according to Table 2 (p. 720).

In two weeks he left the hospital taking 36 units of protamine insulin with a fasting blood sugar of 0.12 per cent and excreting only 5 Gm. of glucose in twenty-four hours. Subsequently he did fairly well, but especially well during 1937, although exceptionally glycosuria appeared temporarily and in fact on February 10, 1937, was 2.2 per cent with a blood sugar of 0.26 (260 mg.) per cent at three quarters of an hour after lunch while on a diet of carbohydrate 180, protein 75 and fat 75 Gm. and protamine insulin 22 units. Throughout the summer he had been especially comfortable and while the diet remained the same the insulin dosage was 24 units. On the evening before his episode he went to a church supper and being meticulous took 1 teaspoonful of baked beans and con-

TABLE 2
CASE No. 14575

May, 1936.	Sugar in urine.		Diet in grams.				Blood sugar, per cent. Time of day.	Insulin units.
	Per cent.	Total grams.	Carbo- hydrate.	Protein.	Fat.	Calories.		
18	9.2						0.49 at office.	
18	7.0							
18-19	11.2	96	66	(1 meal). 26	19	539		[10]
19-20	6.2	81	172	72	68	1588	0.27 11:00	[20] [10]
20-21	5.8	67	172	72	68	1588	0.15 F. 0.25 11:00 0.25 4:00	[30]
21-22	4.1 1.8	45	173	70	68	1584	0.19 F. 0.24 4:00	[40]
24-25	1.1	8	173	70	68	1584		[48]
27-28	0.1	1	171	75	75	1659	0.09 F.	[40]
29-30	1.5	26	173	74	75	1663	0.10 F.	[36]
June, 1-2	0.5	5	149	37	51	1083	0.12 F. 0.23 11:30 0.21 4:00	[36]
1937. June 18	0.1						0.27	[20]
Sept., 22-23	0 0.2	4	138	2 meals. 50	53	1229	0.06 11:00 0.18 4:00	
1938. Jan. 25	0						0.16	[9]

siderable cole slaw (his teeth were artificial and he probably talked much while he ate) in contrast to the usual 50 or 60 Gm. of carbohydrate at such a meal. The next morning he rose as usual, injected his insulin, took a series of gymnastics as was his custom of a lifetime, then a cold bath, followed by shaving and it was after this that he became unconscious and his servants broke into his bathroom. In the following months his tolerance steadily improved and by January, 1938, he required but [9] units to keep sugar-free.

Moral: 1. Always bear in mind a diabetic may improve and need a reduction in insulin, particularly an old diabetic or any diabetic who is doing unusually well.

2. The diabetic who does not consult his physician frequently is taking a chance with his health.

3. No diabetic should allow three quarters of an hour or

an hour to intervene between regular or protamine insulin and breakfast except under close observation with accurate controls to determine the need for so long an interval.

4. In general any diabetic who wishes to defer breakfast for a considerable interval after rising should postpone the injection of insulin to one-half hour before the meal and if both regular and protamine insulin are to be used, the interval should be shortened to fifteen minutes or else the breakfast carbohydrate should be taken at the same time as the insulin.

III. Local Skin Responses: Atrophies of Subcutaneous Fat, Indurations and Allergic Manifestations.—1. *Insulin Atrophies.*—The benefits derived from insulin far outweigh any unpleasant local effects which may follow its use. The latter may be, however, at times so disturbing to the patient as to demand attention. Among the disagreeable skin responses are the atrophies of subcutaneous fat (lipodystrophy) at or near the site of injection. The problem presented by the patient described below is typical.

Miss Dorothy Y., case 15179, twenty-nine years of age, returned on January 14, 1938, for advice as to the prevention and treatment of large depressed areas over both thighs at or near the site of injections of insulin. The onset of her diabetes was in December, 1934, unmodified insulin had been started in the summer of 1935, and since December, 1936, simultaneous before-breakfast doses of unmodified and protamine zinc insulin had been taken. Her insulin requirement lately had averaged 10 units of unmodified plus 30 units of protamine zinc insulin daily. The patient had injected all insulin into the thighs and had made a definite attempt to change the site of injection daily. The doses of unmodified and of protamine insulin had been taken indiscriminately on the two sides. She had noted no abnormality of the skin until the summer of 1937, approximately two years after she had begun to take insulin. The discovery had come at the time of donning a bathing suit; the lesions were well advanced at this time, suggesting that a certain, if not marked, degree of change had been present for weeks or months.

Examination revealed extensive areas of depressions in the skin over the lateral, medial and anterior surfaces of the upper one half to two thirds of both thighs. Quite obviously the

subcutaneous fat in these regions had completely or almost completely disappeared. There was no suggestion of involvement of the muscles or any important structures.

The patient was instructed to shift all injections to the skin of the abdominal wall and flanks, to scatter injections widely over this area and to administer regular insulin entirely on the right side and protamine on the left. The necessity of proper technic in injection with insertion of the needle well below the skin was stressed. Had her dosages been larger, she would have been asked to use insulin of U_{80} or U_{100} rather than of U_{40} strength.

Reports of cases of lipodystrophy due to insulin were published first in 1926 by Depisch¹ and Barborka.² Since then several papers on the subject have appeared.^{3a, b} The characteristic lesion consists of an area of atrophy or disappearance of subcutaneous fat with consequent depression of the skin and alteration of the normal contour of the body in the part affected. Almost invariably the lesions appear at or very near the sites of repeated injections of insulin although in rare instances we have noted what seemed to be typical atrophies in remote parts, as in the face (Case 5127) and submental region (Case 8189).

In our experience atrophies occurring during treatment with unmodified insulin alone are seen frequently in children of both sexes (in about 25 per cent), occasionally in adult females and almost never in adult males. Atrophies may be noted first from within several weeks to many months after treatment with insulin had been instituted; the usual interval from the beginning of treatment is about six months.

As possible causes of this disappearance of subcutaneous fat the following have been suggested: (1) The tricresol which formerly was used as the preservative in insulin distributed commercially;⁴ (2) assumed lipase content of insulin;⁵ (3) trauma of mechanical nature due to the repeated injections, particularly in a restricted area; it has been thought that possibly there occurs damage to "the delicate protoplasmic cell envelope of the fat cells so that fat globules are released, and, acting as foreign bodies in the tissue, result in the formation of histiocytes which take on lipophagic activity";⁶ (4) low-grade inflammation;⁷ (5) Nichol's⁸ sugges-

tion was that "the strong initial concentration of insulin . . . causes an active local oxidation of carbohydrate, which in turn causes an active combustion of local fat"; (6) nerve injury; (7) antiseptics such as alcohol, at times used in sterilizing the needle and syringe.

None of the above-mentioned possibilities have found adequate support in fact. Thus Rabinowitch⁸ found no lipase in insulin; he and Avery⁶ did not believe that the method of sterilization of the needle was at fault; Mentzer and DuBray⁹ and Price¹⁰ found no evidence of inflammatory changes in sections from lesions. Most of the other explanations do not lend themselves well to proof or refutation.

One other possibility has interested us greatly, namely, that the acidity of unmodified insulin ($pH = 2.5-3.0$) may in conjunction with repeated injections of doses of large volume be at fault. Before the introduction of protamine insulin we had tried for a period of seven months a special preparation* of unmodified insulin adjusted to pH 7.4 with a patient (Case 11145) who had suffered marked atrophies with the usual preparations. At the end of the period, well marked lipodystrophy was evident over the half of the abdomen which had received the usual type of insulin whereas a much less striking, though unmistakable, lesion was present over the over half into which the neutral insulin had been given.

An excellent opportunity to test the importance of the reaction of insulin in the causation of atrophies has been afforded in the use of protamine insulin with approximately 2000 patients since August, 1935, because the protamine insulin in use at the present time is adjusted to pH 7.3. Our experience to date suggests that the incidence of such atrophies has been greatly lessened although they do occur. We realize that further observation may alter present impressions but the results to date are striking. As an aid in the interpretation of results, we have asked all patients taking both types of insulin to inject the regular (unmodified) insulin on the right half of the body and all the protamine insulin on the left half. If a sufficient number of patients can be prevailed upon to follow

* Kindly supplied by Eli Lilly and Co. The preparation which we used was prepared originally at the request of Drs. Fischer and Ottenberg of New York who carried out tests with it.

strictly such a plan, careful reports during the coming months should answer the question at hand.

The factor of the trauma incident to repeated injection of large amounts of fluid should be kept in mind and since with protamine insulin, the number of injections daily are fewer and with U₈₀ strength the volume of fluid smaller, these facts should be allowed proper weight in the interpretation of results.

Fortunately if, when areas of fatty atrophy have developed, injections in these regions are discontinued for an indefinite period, almost invariably fatty tissue will gradually fill in and the lesion gradually disappear. The restorative process may require two years or longer.

2. *Indurations due to Insulin.*—When patients unwisely inject insulin, unmodified or protamine, repeatedly into a single small area, there may develop in time not an atrophy of the subcutaneous fat but a thickening and hardening of the skin and subcutaneous tissue in that area. These indurated areas have been called "tumefactions," "insulin lumps," "insulin pads" or "lipomatoses." They may be but usually are not tender to touch. The patient comes to prefer these areas for injections because less pain occurs than in fresh areas. Absorption from such regions is not normal, however, and the full effect of the dosage taken may not be secured. Furthermore, local resistance to infection apparently becomes less since these areas are favorite sites for abscesses occasionally seen at the site of injections of insulin. Patients must be made to shift injections from one place to another so that no small area receives insulin oftener than once in every three or four weeks.

3. *Allergic Manifestations.*—As an intimate part of its structure, unmodified insulin carries with it protein derived from cattle and in some preparations, hogs. Protamine insulin contains not only this but also protein from fish. It is small wonder then that patients who are started on protamine insulin often develop small areas of swelling, redness and tenderness at the site of injections. Itching may be a feature. Usually such local responses appear within a few or several days after protamine insulin has been started and may continue for several days or even a few weeks. Any individual response begins within a few minutes after the injection of a dose of

insulin, may last several hours and not entirely disappear for a day or two.

The important point to bear in mind is that success in treatment lies in continuing injections day after day, since in our experience almost invariably the local responses gradually become less and less and finally no longer occur. Occasionally one may be tempted to discontinue protamine insulin and to return to the regular variety because of the annoyance of the allergic reactions but if one explains the situation to the patient and persists in treatment, the local responses eventually cease to be a problem.

IV. Evaluation with Children as an Index.—The convenience and comfort of the single time technic in the administration of protamine insulin have made it valuable from the patient's point of view but the test of its efficacy as a great therapeutic agent in severe diabetes rests with its effect upon the reduction of mortality rates in juvenile patients; the better control of diabetes, measured by the behavior of the blood sugar, urine sugar and blood fat; the promotion of the physiologic processes such as growth and development and gestation; the prevention of the progression of severity of diabetes and the prevention of the pathologic complications of the disease.

The mortality of the 604 juvenile patients treated with protamine insulin between September, 1935, and September, 1937, has been 0.7 per cent. There were only 4 deaths and 2 of these were due to coma, one to an automobile accident and one to a cause unknown.

The better control of diabetes as measured by blood sugar and urinary sugar, need no comment here. They were reported by Dr. Hagedorn and his co-workers in January, 1936, and many of the early tests were done upon juvenile patients. These results have been confirmed by all physicians using protamine insulin in large numbers of cases and over a long period of time.

The prevention of the progression of diabetes is suggested by the average ratio of insulin per kilogram of body weight, which in our juvenile patients in 1936 was 1.3 and in 1937 1.2. However, the average durations of diabetes in these two periods were six and seven years, respectively. Both figures represent the time when stabilization of the disease has generally

occurred. In order to obtain a better picture of the effect of protamine insulin upon the progression of diabetes we have compared new cases treated in 1935 to 1936 and find that their average dose of insulin was 39 compared with 38 in 1937.

Degenerative complications such as arteriosclerosis, cataracts and retinal hemorrhages have not often occurred in the juvenile patients under the fifth year of duration. Therefore, since protamine insulin has been used in this country only since September, 1935, an insufficient time has elapsed to assure us that the patient is protected against the development of these complications; on the other hand we do have instances of the disappearance of retinal hemorrhages since the use of protamine insulin. Thus, one patient, Case No. 6884, the duration of whose diabetes is now 9.8 years, and whose diabetes had been uncontrolled during this period, was reported by Dr. J. H. Waite to have retinal hemorrhages in December, 1934. Protamine therapy was started in January, 1936. In January, 1937, and November, 1937, twelve and twenty-three months after the use of protamine insulin, her eyes were said by the same examiner to be normal.

Infections of the skin, urinary tract, and chest have been common in our diabetic children. One new instance of pulmonary tuberculosis, Case No. 10020, has occurred in our juvenile series. There have been no new cases of urinary tract infection and only 6 serious infections of the skin.

Skin complications, too, have been exceptional. Thus xanthosis, xanthoma and necrobiosis lipoidica diabetica have not been recognized in patients newly treated with protamine. Xanthomata we would not expect often because of the accurate control of fat metabolism; this complication is definitely related to hypercholesterolemia. The average plasma cholesterol for our children treated with protamine insulin was 202 mg. per 100 cc. Hypercholesterolemia, however, does occur even among children treated with protamine insulin and 20 per cent of our cases have had values above 230. In one patient, Case No. 6310, whose diabetes was of ten and one-half years' duration and who had a chronic ulcer in a necrobiotic lesion for a period of eight years, the ulcer healed within four weeks of the time that protamine therapy was started.

The most dramatic change, however, has been in the re-

duction of hepatomegaly. Significant enlargement of the liver has been recognized in 65 of our juvenile patients. Twenty-two have been treated with protamine insulin and a reduction of the size of the liver has occurred in 80 per cent of the cases so treated. The most remarkable reduction was that of Case No. 12166, whose diabetes was severe of four and one-half years' duration. In the four years of her diabetes she had had three attacks of diabetic coma but during the past two years the disease had been under reasonably good control. She was known to have hepatomegaly for a period of eighteen months. Within six weeks of the time that protamine therapy was started a reduction in the size of the liver was noted. The measurements prior to and six weeks following the start of protamine therapy are as follows: the long diameter decreased from 25.5 to 21 cm. and angle of liver from 63° to 53° . The reduction in the size of the liver with protamine therapy has been a definite contribution to our knowledge of the mechanism of this lesion. There have been no autopsies or biopsies among our juvenile patients with this lesion. In the experimental laboratory hepatomegaly has been produced by the injections of anterior pituitary substance, or by the omission of choline from the diet. However, many of our diabetic children with hepatomegaly had dwarfism and must have had a lack rather than an excess of anterior pituitary and the choline content of the diet was high rather than low. The latter, however, does not exclude failure of utilization of choline, but the evidence is in favor of a mechanism related to faulty control of diabetes because the recovery has been so rapid and dramatic when the disease has been better controlled with protamine insulin.

The incidence of coma in the era of protamine insulin has been very low. Thus, among our entire series of juvenile patients nearly a third have had one or more attacks of it and the most recent incidence has been one or more attacks in 1 out of every 10 diabetic children. Yet among our 604 patients treated with protamine insulin there were only 18 or an incidence of 3 per cent. The causes of coma, such as dietary indiscretion, infections and the omission of insulin persist, but the margin of safety is far greater because protamine insulin remains in the body not only twenty-four but forty-

eight hours or even longer. A protection against the resistance to insulin which occurs during fevers and against results of dietary indiscretions is assured. Practically speaking there was only one cause for diabetic coma among children treated with protamine insulin and this was the omission of insulin which had occurred in 80 per cent of the 18 patients who contracted this complication.

Thus protamine insulin has solved many pathologic complications of juvenile diabetes and a failure of therapy must be challenged on the basis of abnormal psychology or physiology. We have 2 juvenile patients who represent failures of the former type. Thus Case No. 6884, on whom fully \$8,000 of public or charity funds have been spent for medical care since the onset of her diabetes in 1928, and Case No. 9148, whose parents have spent an almost equal amount, do not represent successes with protamine insulin therapy. The first patient has had three attacks of diabetic coma since the use of protamine, but she was a notorious malingerer about symptoms and fever, and in spite of asking daily advice about her dosage of insulin, regularly omits it or uses much less than the amount prescribed. The second patient was taken off protamine insulin because of presumed violent insulin reactions. However, it was later appreciated that these were simulated, and during another episode it appeared as if regular insulin too was not successful but that she was definitely resistant to it. In spite of presumed large doses of insulin in the home of a nurse well versed in the treatment of diabetes she developed diabetic coma, which progressed in turn although at half-hourly intervals enormous quantities of regular insulin were administered. This patient was not truly resistant to regular insulin for she had inserted water into the insulin bottles when unobserved.

Physiologic problems in the young diabetic, namely those connected with growth and pregnancy, we do not expect to be solved by protamine insulin. We have had enough experience with anterior pituitary preparations containing the growth factor used with and without protamine insulin to attribute the dramatic change which we see in the growth curve of the child to the pituitary factor rather than protamine insulin. The three accidents of pregnancy, miscarriage, stillbirth associated

with toxemia, and neonatal death in our experience have not been related to or predicted by disturbances of diabetes *per se* or to the lack of control of the disease, but are definitely related to and predicted by an abnormal balance between prolan and estrin.

Just as the juvenile patient has revealed the advantages of regular insulin and in comparison its minor defects, so, too, it has revealed the advantages and in comparison the minor defects of protamine insulin, which are largely its cumulative action and the slow release of active insulin from protamine compounds. The former leads to severe insulin reactions and the latter to the need of an accessory dose of regular insulin. But its success is attested to by the better control of diabetes, the fact that only 2.8 per cent of our juvenile patients who have been started with protamine insulin have given it up in preference to the many doses of regular insulin, the reduction of the incidence of coma and of hepatomegaly.

V. Use in Surgery, Pernicious Anemia and Hyperthyroidism.—Protamine zinc insulin is particularly valuable in the presence of complications, notably illustrated by surgical operations and pernicious anemia. Anemia itself is a frequent accompanying feature of diabetes, particularly in the presence of conditions requiring surgery with or without infection. It is important to realize that often in the surgical diabetic the proper use of liver extract and vitamin therapy may aid the effectiveness of protamine zinc insulin, and the combination renders surgical procedures vastly more safe. The following cases are reported as illustrating the effectiveness of protamine insulin in diabetes with pernicious anemia and hyperthyroidism.

Case I (9920), housewife, age forty years at the discovery of glycosuria by her husband, a physician, in 1907. Marked polyuria and polydipsia did not develop until 1930, no doubt postponed in part by dietary treatment during the intervening period. Her mother died of pernicious anemia. The patient had weighed 123 pounds in 1914. In 1919 she developed acute hyperthyroidism which was relieved by x-ray treatment. In 1925 pernicious anemia was diagnosed and treatment begun by Dr. G. R. Minot. Use of regular insulin was begun in March, 1931, and continued thereafter. Her body weight at that time was 87 pounds, blood pressure 130/70, pulse rate

was regular, heart considerably enlarged with a systolic murmur, lungs and abdomen normal. In January, 1937, she returned to the Deaconess Hospital, the urine containing 6 per cent sugar, and the use of protamine insulin was begun. At this time auricular fibrillation and evidences of beginning cardiac failure were present for the first time. Her body weight had fallen to 78 pounds, basal metabolism was plus 43 per cent, and she was clearly suffering from hyperthyroidism. Lugol's solution was begun and, as the basal metabolism fell, control of the sugar became easier so that the dose of protamine insulin, which had formerly been 34 units a day without rendering the urine completely sugar-free, was reduced to 20 units.

Because of the severity of the hyperthyroidism, the operation was carried out by Dr. F. H. Lahey in three stages. In the first stage on February 17 a bilateral ligation of the superior poles of the thyroid was done without serious upset although the pulse rate was extremely rapid and the patient was somewhat toxic, requiring frequent intravenous glucose injections during the first twenty-four hours.

She returned to the hospital on March 21, 1937, when a right subtotal hemithyroidectomy was done. At this time the table (p. 731) gives a record of her diabetic treatment for the three days prior to operation and until discharge eight days after operation.

The wisdom of the three-stage operation was shown by the fact that following operation she vomited repeatedly for two days. On the day following operation she was unresponsive. It may be noted from the chart that she had two blood sugar values of 0.04 per cent in spite of four injections of intravenous glucose solution, illustrating again the ease with which diabetic patients may develop hypoglycemia in the presence of hyperthyroidism.

The left subtotal hemithyroidectomy was done on May 19, 1937, without serious upset. She received four intravenous injections of 1000 cc. of normal saline with 10 per cent glucose solution on the day of operation.

She returned to the hospital on December 15th in good condition, the weight had risen to 90 pounds, the basal metabolism at its lowest level on December 21, 1937, was minus 10

CASE 1

 HEMITHYROIDECTOMY IN A DIABETIC WITH PERNICIOUS ANEMIA AND
AURICULAR FIBRILLATION

Date.	24-hour urinary sugar (Gm.).	Diet.				Blood sugar, per cent.	Pro- tamine zinc ins.	Regular ins.
		Carbo- hydrate (Gm.).	Protein (Gm.).	Fat (Gm.).	Calories.			
1937 March 21-22	9	57	21	24	648	0.24—7 P. M.	24	5
22-23	18	151	60	73	1501		24	
23-24	46 I. V. 750 cc. saline and 10 per cent glucose.	155	61	75	1539	0.22—11 A. M. 0.24—4 P. M.	24	4
24-25	21 I. V. 750 cc. saline and 10 per cent glucose. I. V. 1000 cc. saline and 10 per cent glucose. Right subtotal hemithyroidectomy, March 24.					0.19—11 A. M.	20	20 15 15
25-26	18 I. V. 1000 cc. saline with 10 per cent glucose.	99	14	20	632	0.04—7 A. M.	20	20 15
26-27	0	108	29	45	953		20	
27-28	31	152	45	86	1562	0.04—7 A. M.	20	5 10
28-29	19	163	46	74	1502		20	10
29-30		161	62	75	1567		20	
30-31	31	166	71	77	1641	0.27—7 A. M. 0.30—11 A. M. 0.28—4 P. M.	24	
31-1	5	163	71	78	1638		28	4 6
April 1	0	166	67	79		0.07—7 A. M.	28	

per cent. The pulse rate was 90, she had no edema, an acute upper respiratory infection was responsible for a number of râles in the right lower chest. At this time she improved rapidly and left the hospital taking a diet of carbohydrate 132 Gm., protein 61 Gm., fat 81 Gm. and calories 1497 with 28 units of protamine insulin once a day.

The anemia has been controlled since 1931 by the use of liver extract by mouth. Originally her red blood count was 1,800,000. During the last six years it has varied from 4,180,000 to 5,300,000 and hemoglobin from 82 to 98 per cent. The red blood cells do show slight variation in size and shape.

Case II (13969), housewife, aged fifty-eight years at onset of diabetes in June, 1931. She first entered the Deaconess Hospital August 31, 1935. At this time a large goiter was present, heart, lungs and abdomen were essentially normal except for a large liver, the edge of which could be felt 5 cm. below the

costal margin. At this time the red cells numbered 4,500,000; hemoglobin 82 per cent, white cells 8450. The urine contained 1.7 per cent sugar, blood sugar was 0.29 per cent. A subtotal thyroidectomy was carried out September 14, 1935, by Dr. F. H. Lahey without difficulty, the patient requiring 60 units of insulin given in small doses of 5 to 20 units every three to five hours during that day. She left the hospital in good condition, taking a diet of carbohydrate 140 Gm., protein 56 Gm., fat 81 Gm. and insulin in dosage of 18 units before breakfast, 18 units before the evening meal and 4 units at bedtime. Even with this amount of insulin the blood sugar values were high, and indeed on the day she left the hospital it was 0.33 per cent before breakfast. She did well at home, however, and in December, 1935, was sugar-free, the blood sugar was 0.20 per cent on the same diet and insulin of 32 units a day. At this time a basal metabolism was plus 4 per cent.

In May, 1936, the skin appeared somewhat yellow, she was dyspneic on exertion and had repeated vomiting. A gastric analysis showed no free hydrochloric acid in any specimen but the red cells numbered 4,830,000. In May, 1937, the use of protamine insulin was begun and the urine sugar was well controlled with the use of 4 units of regular insulin before breakfast and an additional dose of 36 units of protamine insulin, in place of the three injections of regular insulin which she had been using. In June of this year she gave up the protamine insulin and went back to regular insulin chiefly because she had had a mild insulin reaction. When she returned to the hospital on December 5, 1937, the urine contained 1.4 per cent sugar and the blood sugar was 0.33 per cent, fasting. At this time she had been taking 34 units of regular insulin divided into three injections before each meal. The red cells numbered 2,750,000, the hemoglobin 58 per cent, white cells 4800, and the stained smear showed moderate variation in size and shape of the red cells. The individual cell volume was 12×10^{-11} . Injections of liver extract intramuscularly were begun immediately. As the anemia diminished, the diabetes improved strikingly. During the first five days of her hospital stay the urine did show a considerable amount of sugar, the blood sugar values were high, even when the insulin dose was increased to 50 units a day. Then, however, during the last

ten days of her hospital stay all the urine specimens were sugar-free, the blood sugar values fell and we were finally able to discharge her from the hospital with a single dose of 36 units of protamine insulin before breakfast with all specimens sugar-free.

Other interesting symptoms were present: the tips of her fingers and toes were numb, and tingling sensations were present. The tongue felt swollen, as if it were too large for the mouth; a typical glossitis was present. Actually within a few days of the inauguration of treatment with liver extract the tongue seemed to be reduced in size, the typical smooth, raw, red appearance changed for the better and the sensation of swelling disappeared.

Although the cases are few, we have seen more than one instance such as Case II in which a surprisingly rapid transition from the condition of hyperglycemia and marked glycosuria was obtained when protamine zinc insulin was used in place of regular insulin. The explanation is not clear unless here again the more steady favorable influence of protamine zinc insulin upon liver function is responsible. It is true that these patients were given rather vigorous treatment with liver extract and iron. It has been suggested that vitamin therapy, notably vitamin B₁ therapy, favorably influences insulin activity. Aszodi and Mosonyi,¹¹ as well as Martin¹² and Lajos¹³ and Vorhaus¹⁴ have studied this question experimentally. It seems reasonable that a liberal administration of vitamin B₁ should be desirable in diabetes particularly because of the well-known deficiency of the external pancreatic secretion in most cases of moderate or severe diabetes. This deficiency in the external pancreatic ferments may be responsible for failure of the combination between the intrinsic or gastric factor which protects against pernicious anemia and the extrinsic or dietary factor. At least this seems a possible explanation for the striking frequency of anemia both of secondary and primary types.

Advantages of Protamine Zinc Insulin in Surgery.—During 1937, operations upon 187 diabetic patients have been carried out at the Deaconess Hospital, all of whom received protamine zinc insulin during operation and for treatment after operation. Among the 187 operations were included 52

amputations, 31 laparotomies, 18 tonsillectomies, 13 thyroidectomies, 6 nephrectomies and 66 miscellaneous. Advantages of protamine zinc insulin during surgery have been manifest in the following ways:

1. Its constant slow action when given before operation in the morning protects the patient against the possibility of an insulin reaction occurring during the anesthesia when the surgeon might not recognize the symptoms. In none of the patients mentioned here has an insulin reaction occurred during operation, although it is true that with regular insulin we have had such an accident.

2. The slow steady action of protamine insulin means a constant protection of liver function inasmuch as it enables the liver to form glycogen and prevents the abnormal transformation of protein and fat in the liver with the production of acidosis during anesthesia and later, especially if vomiting should occur.

3. With protamine zinc insulin large quantities of carbohydrate can be utilized both before operation and after. Particularly in cases of severe hyperthyroidism this utilization of large quantities of glucose is a protection to liver function of major importance. In Case I described above, by consulting the chart it will be seen that in three days, including the day before operation, the day of operation and the day after operation, the patient received 350 Gm. of glucose as glucose solution given intravenously plus 254 Gm. of carbohydrate in the diet or a total of 604 Gm. of carbohydrate. Of this amount only 85 Gm. were excreted in the urine in spite of the operation, the anesthesia and the glucose administration. It is true that the skilful administration of cyclopropane as an anesthetic with its high oxygen content undoubtedly is helpful in protecting such patients. It is to be noted that this patient was discharged April 1st, only eight days after the operation.

4. The danger of serious hypoglycemia following operation, particularly when intravenous glucose solution has been administered, is lessened by the use of protamine zinc insulin. Whereas formerly occasionally serious insulin reactions occurred when regular insulin was used together with glucose solution, with protamine zinc insulin we have had no serious reactions following operation. In Case I, which has been

selected because it illustrates rather an excessive use of insulin and moderate hypoglycemia following operation, it is notable that even with a blood sugar of 0.04 per cent there were no serious symptoms. It is true that the patient was extremely drowsy at the time of this low blood sugar but she became alert immediately upon the administration of the glucose solution which had been planned.

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CLINIC OF DR. J. H. MEANS

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UPPER GASTRO-INTESTINAL HEMORRHAGE

EACH year when I am doing my regular block of general medical ward visiting I am impressed with the magnitude of the problem presented by hemorrhage from the upper gastrointestinal tract.

Let me present some of the cases encountered on my last tour of duty to illustrate the vicissitudes of diagnosis in such cases and the perplexities of treatment. I will touch but briefly on each case, attempting merely to give emphasis to its salient features.

Case I.—A man of fifty-six was brought in by a police ambulance for massive hematemesis beginning an hour before he arrived at the hospital. There had been a similar episode eleven weeks earlier. There was also a five-year story of midepigastria, nonradiating distress on occasions, two to three hours after meals and relieved by food or soda. This symptom had slowly been getting worse. There had been no weight loss.

He was pale and in shock on arrival, his blood pressure being 90/70 and his red count 3,600,000. He received an emergency transfusion and the next day was much better. Nothing important was made out on physical examination. We refrained from palpating the abdomen vigorously.

Diagnosis.—The character of the hemorrhage, the five-year, rather classic story, the absence of weight loss, all made us think first of bleeding peptic ulcer. Since he admitted to some considerable alcohol intake, bleeding esophageal varix due to portal cirrhosis was also considered.

x-Ray examination was considered safe on the sixth day in hospital. To our astonishment it showed in the center of the stomach a lobulated, smooth, oval defect, 8 cm. long and 4

cm. wide. The mucosal folds in the region of this lesion were difficult to demonstrate without palpation (forbidden because of the recent bleeding), but in several films it appeared that the mucosa was intact in the greater portion of the diseased area. It was thought that the lesion arose from the lesser curvature and posterior wall and that it had a pedicle 5 cm. in diameter. There was a deep ulceration in the lesion between 1 and 2 cm. in diameter. The remainder of the stomach, pylorus and duodenum were normal. The roentgenologist considered the findings fairly characteristic of neurofibrosarcoma or leiomyosarcoma.

Knowing that leiomyoma of the stomach may run a rather chronic course and give rise to recurring profuse hematemesis, we inclined to accept the roentgenologic diagnosis. This led us again into error.

Operation was performed four days after the x-ray examination, the patient having been prepared by two more transfusions, about 500 cc. each, given by the slow drip method, and a high vitamin intake.

The surgeon found a fungating growth situated on the lesser curvature of the stomach and occupying most of the posterior wall. It was sharply circumscribed, round in contour and about 8 cm. in its greatest diameter. It had a central crater-like ulceration about 0.4 cm. deep. It was firm in consistency and the serosa over it was unpuckered. No enlarged glands or evidence of infiltration were discovered. The surgeon performed a subtotal gastric resection, a posterior Polya anastomosis and an entero-enterostomy between the proximal and distal arms of the jejunal loop.

The final diagnosis, made histologically by the pathologist, though suspected in the gross by the surgeon, was adenocarcinoma.

The patient made a good recovery and was discharged two months before the present writing. He was seen two days ago and was continuing to do well.

Comment.—This case, then, appeared at first sight to be one of bleeding peptic ulcer, by x-ray leiomyoma, and finally turned out to be adenocarcinoma of the stomach. In retrospect there seems nothing to criticize about the management, except that a gastroscopy might have given the correct diag-

nosis preoperatively. The final outcome is, of course, uncertain but there is a possibility that he has been cured.

Case II.—A truck driver of thirty-six, on January 5, 1937, having been previously quite well, had a copious hematemesis. His physician put him to bed for three weeks and on a dietary régime for peptic ulcer. On January 26, 1937, he was x-rayed in this hospital. The esophagus and duodenum were negative. The rugae of the stomach showed marked hypertrophy. At this time his red count was 4,100,000 and his hemoglobin 70 per cent. A bland diet was prescribed and he was not seen again until September 27, 1937. On this occasion he entered the hospital for a second profuse hematemesis which had begun forty-eight hours earlier. He had been well in the interval preceding this episode. The degree of blood loss is indicated by his red count of 2,500,000 and 50 per cent hemoglobin. He was transfused at once, but this did not improve his blood picture. In fact, his red count sank to 2,000,000 and his hemoglobin to 45 per cent. This may have been in part due to the making up of blood volume by fluid, but also in part to further hemorrhage.

Diagnosis.—It was on October 1, 1937, that I took charge of the patient. I was strongly inclined to a diagnosis of ulcer in spite of the previous x-ray evidence of hypertrophic gastritis. The severity of the hemorrhage was what chiefly influenced me. The man admitted to the use of a moderate amount of alcohol, so that cirrhosis was also to be considered. No evidence for it was obtained on physical examination, in fact, the physical examination was essentially negative save for pallor.

Progress.—For a week the man continued to have successive hematemeses for which repeated slow drip transfusions of citrated blood were given.

x-Ray examination was made on October 14. At that time he had stopped bleeding and was doing well. The roentgenologist found considerable change since the previous examination. The rugae of the stomach were still grossly irregular, but presented a mangled appearance instead of a rather regular hypertrophy of the folds. The greater curvature showed an accumulation of barium between folds of mucosa simulating a large irregular crater. but the radiologist could not say defi-

nately that an ulceration was present. The duodenum also showed gross thickening of the mucosa but no crater.

This examination left us still in a quandary as to whether he had gastritis or peptic ulcer or both. We therefore asked Dr. E. B. Benedict to perform gastroscopy. This was done on October 16. A good view was obtained. The pylorus appeared normal and tightly closed. Peristalsis was active. There was some slightly blotchy reddening of the mucosa of the antrum, and the rugae were tortuous and reddened. On the anterior wall near the cardia there was a superficial ulcer about 2 cm. in diameter. Its base was white and smooth. Its margins were sharp, smooth and bordered with red. No bleeding was observed. Dr. Benedict's diagnosis was gastric ulcer and hypertrophic gastritis.

The patient continued to do well on a frequent-meal, bland diet on which he was discharged November 6, 1937.

On November 29, 1937, he came in for check-up. Reexamination by x-ray still showed thickened gastric rugae in the region of the greater curvature. Again the duodenum was irregular and the roentgenologist concluded that a duodenal ulcer was present in addition to the other lesions, but no crater was demonstrated. He was progressing well symptomatically.

Comment.—The interesting features in this case are, first, that we didn't know in the beginning whether he had ulcer or gastritis. It turned out that he had both, and two ulcers apparently at that, one in the stomach, one in the duodenum. It seems fair to suppose, however, that all these lesions are manifestations of a single fundamental morbid process. From which lesion he bled was not determined.

From the therapeutic side also the case is interesting. We were concerned chiefly with whether to operate, and in addition to transfusion what medical measures should be taken. As to operation we feel in this clinic that it is rarely necessary to operate for first hemorrhage in persons under fifty. This patient was under fifty. We also believe that recurrence of hemorrhage increases the indication for operation. This man had had one previous hemorrhage. When he first came in we considered that it was quite proper to carry on with medical procedures, because he was relatively young and because his previous hemorrhage had promptly stopped. After he had bled

repeatedly for a week in our wards, surgery was carefully considered and decided against on the ground that patients operated after a week of bleeding seldom do well. The chance without operation was thought to be better than with. Of medical measures the chief one under debate was diet. Meulengracht has reported remarkably good results from treating gastric bleeding with food. The neutralization of digestive juices by food is of more importance in hemostasis than is the avoidance of any mechanical hindrance food might produce. We have gone part way along Meulengracht's path, and may yet go the whole way. Certainly we feed earlier and more in gastric hemorrhage than we did a few years ago.

In the present case it is interesting to record that on the sixth day in hospital the patient said, "Say, Doc, why don't you quit pumping blood into me and give me something to eat? Then I might get well. When I had my first hemorrhage my doctor let me eat and my bleeding quickly stopped." The wise physician does not let himself be too resistant to suggestions made by patients. In this case we followed the patient's advice and it was the turning point in his progress. Whether the ensuing improvement was the result of the change in therapy or would have occurred in any event, no one can say.

Let us next consider the cases of two youths, each showing bleeding from the alimentary tract.

Case III.—A boy of fourteen had recently been in the orthopedic ward for two months where he had been operated upon for the lysis of adhesions involving his right peroneal nerve and the removal of an exostosis of the right femur, which lesions had occasioned some pain in his leg. While there he had developed recurring attacks of vomiting, associated with central abdominal pain, which had increased in severity following his discharge. At the same time he lost weight and strength and developed pallor.

On September 20, 1937, he was admitted to the medical ward for study. The physical examination was noncontributory and the blood showed only a slight anemia (red blood corpuscles, 4,700,000; hemoglobin, 70 per cent).

Diagnosis.—It was thought that his symptoms might be on a functional basis until a strongly positive guaiac test was obtained from a stool. Gastro-intestinal x-ray was then ordered

and, to everyone's amazement, showed a constant deformity of the first portion of the duodenum with an ulcer crater, 1 cm. in diameter, in the middle of it. The stomach and esophagus were normal.

Progress.—He soon became asymptomatic on medical régime and his nutritional state was improved. A second x-ray, taken two weeks after the first, however, showed no diminution in the size of the crater. The plan is to continue with medical régime as long as progress is satisfactory.

Comment.—The interesting points in this case are:

1. That typical duodenal ulcer may occur and may give rise to bleeding in a child of fourteen.
2. That the diagnosis wasn't suspected until occult blood had been found in the stool.

Case IV.—A seventeen-year-old college freshman came in with the story of having been perfectly well until three days before, when without warning he had a brisk hematemesis, following which he felt rather dizzy. On arrival in hospital he was practically symptomless, but showed pallor and an anemia of red count 2,800,000, hemoglobin 57 per cent. His stools were tarry and gave a strongly positive test with guaiac. We thought that he probably had a bleeding peptic ulcer.

He was treated with a frequent-meal, soft diet, iron and complete rest in bed.

On the fifth hospital day, a barium examination was made in the horizontal position and without manipulation. No evidence of disease of esophagus, stomach or duodenum could be found.

We therefore invited Dr. E. B. Benedict to perform gastroscopy.

Gastroscopy was done on the fourteenth day in hospital. Dr. Benedict found the gastric rugae of normal size throughout, but with very marked reddening and superficial erosion on the crest of several folds, especially high up on the posterior wall near the cardia. No actual bleeding point was seen. There was a definite verrucous appearance of the mucosa in these areas and also along the lesser curvature. There was a moderate amount of mucus present, and in the region of erosion there was some inflammatory exudate.

Dr. Benedict's diagnosis was superficial and hypertrophic gastritis.

On the fourteenth hospital day he ceased to show a positive guaiac test on the stool and on the nineteenth a repeat barium examination, with all maneuvers permitted, showed no lesion in the gastro-intestinal tract.

A month after discharge he was entirely asymptomatic.

Comment.—An interesting illustration of how closely gastritis can simulate ulcer and how it may be totally unproductive of symptoms until the moment of major hemorrhage.

A somewhat similar case but in an older man is represented by the following:

Case V.—An Italian of forty-four had had his gallbladder out at another hospital three years previously. For many years he had vague abdominal distress, usually relieved by bland food and never severe enough to cause him to seek medical advice.

Two days before entry he had had a happy holiday of fishing, which included a fall into the lake and a 60-mile drive home in wet clothing. He felt well the next day until noon when, without warning, he had a large hematemesis followed by faintness.

The day of entry he had passed tarry stools.

Physical examination disclosed nothing of importance and the roentgenologist on the third hospital day could find no evidence of disease by barium examination in the esophagus, stomach or duodenum.

His degree of blood loss was only moderate, the red count standing the first few days at 3,500,000 and the hemoglobin at 60 per cent.

Since a diagnosis had not been established, we called on Dr. Benedict again, who performed gastroscopy on the thirteenth hospital day.

Gastroscopy showed that just proximal to the musculus sphincter antri on the lesser curvature the mucosa presented a markedly verrucous appearance with warty elevations ranging from 2 to 3 mm. in diameter and height. In this region on the lesser curvature was an oval shallow erosion about 8 mm. in diameter and 1 mm. deep with a clean, whitish base. It appeared to be healing. The folds of the lesser curvature

appeared normal except for one or two which had a slightly beaded appearance.

Dr. Benedict's diagnosis was hypertrophic gastritis with erosion.

The man made an uneventful recovery on bland, many-meal diet with iron. Seen a fortnight after discharge, he was quite asymptomatic.

Comment.—Another example of fairly impressive hemorrhage attributable to gastritis.

Case VI.—A man of fifty-nine, one month before entry had had, without previous symptoms of any sort, acute epigastric pain immediately followed by the vomiting of thin black material and three hours later by the passage of a tarry stool. The melena continued for several days and he vomited material looking like coffee grounds on several occasions. A rather continuous epigastric gnawing also appeared and persisted. Vomiting became increasingly frequent—several times daily. He placed himself on a bland diet as he found that was the only one that would stay down at all. He became constipated and rapidly lost weight.

Physical examination at entry disclosed nothing of great importance beyond pallor and dryness of tongue and mucous membranes. The stool was dark colored and gave a strongly positive guaiac test. The blood picture was 3,500,000 red cells and 50 per cent hemoglobin. The blood pressure was 140/90.

Diagnosis.—Because of his age, the character of the bleeding and the brevity of the story, I was strongly inclined to a first choice, speaking diagnostically, of cancer of the stomach. It was evident also that he had some degree of pyloric obstruction with gastric stasis, either functional or organic, and malnutrition and dehydration. He was not a user of alcohol, and I did not seriously consider cirrhosis of the liver. My resident put ulcer first in differential diagnosis.

He was given a transfusion of blood by the slow drip method, and on account of his obstruction was treated with intravenous fluids only and full doses of atropine for the space of forty-eight hours. Then he was started on fluids by mouth, but continued to vomit. On the sixth day it was decided to have x-rays taken.

x-Ray examination showed the esophagus to be normal. There were no varicosities to be seen. The stomach was normal in appearance. The first portion of the duodenum was grossly deformed and showed an irregular constriction near its apex. No crater was made out, nevertheless the roentgenologist considered the appearance characteristic of ulcer.

Dr. A. W. Allen, of the surgical service, was consulted and advised operation on the ground that the man had obstruction and persistent bleeding. He considered him suitable for posterior gastro-enterostomy.

Operation was done on the thirteenth day in hospital, directly after a blood transfusion. A small duodenal ulcer was found with surprisingly little induration about it. The stomach showed very marked gastritis. A posterior gastro-enterostomy was performed. On the twelfth postoperative day the patient died of bronchopneumonia. Autopsy permission was sought, but refused.

Comment.—In view of the operative findings, it seems likely that the bulk of this man's symptoms were on the basis of gastritis. In retrospect it is evident that we should have performed gastroscopy. Had this been done, the gastritis, not shown by *x-ray*, would have been disclosed and recognized as a likely source of bleeding and cause of vomiting. Had the discovery been made in time we might not have permitted operation and he might be living today.

An error in diagnosis led to an error in treatment. The diagnostic procedure which might have led to a correct diagnosis was not made use of. All of these facts have a high educational value.

Case VII.—A man of seventy-one entered with a story that eight months before he had suddenly, after physical exertion, raised two mouthfuls of blood. It was not clear whether this came from the trachea or esophagus. A month later he began to have edema of his ankles. This gradually increased, extending up his legs, and for two months he had had in addition a progressive enlargement of his belly. He claimed to be a teetotaler.

Physical examination disclosed an emaciated old man with sclerotic ocular fundi, dulness and diminished breath sounds at both lung bases and an abdomen very distended and tense

from ascites. The legs showed pitting edema to the knees. On the day following admission he vomited some coffee-ground-like material giving a strongly positive guaiac test.

The urine was not remarkable. The blood showed a moderate normochromic anemia, a white count of 5300 and one stool out of three gave a positive guaiac test.

Abdominal paracentesis produced 3 liters of pale yellow fluid, specific gravity 1.009.

Diagnosis.—His dropsy did not yield to digitalis and it was concluded that it was not in any important degree of cardiac origin. Tapping and the use of salyrgan kept his ascites in check somewhat, but nevertheless he steadily failed. In spite of his statement that he used no alcohol we concluded that he probably had cirrhosis of the liver. His Wassermann was negative.

Under observation he became increasingly icteric. On the seventeenth day in hospital he had some spasmodic abdominal pain, following which he vomited about 3 ounces of bright blood. A few hours later he passed some blood by rectum. The following day he died.

The autopsy showed that he did have cirrhosis of the liver. It was of the toxic type and there had been an episode (asymptomatic) of acute yellow atrophy in the past. This was quite healed but the liver weighed but 760 Gm. The abdomen contained 2000 cc. of clear fluid. No collateral circulation was observed. The esophagus showed no varices. The stomach was normal save that it contained coffee-ground material. The duodenum showed a deep punched-out posterior wall ulcer 1.5 cm. in diameter.

Comment.—The surprising thing in this case was that, although we were quite correct in supposing that he had and that he died of cirrhosis of the liver, the source of hemorrhage from the gastro-intestinal tract was not, as one would suppose, in the presence of cirrhosis, an esophageal varix, but a totally unsuspected duodenal ulcer. The pathologist was quite certain that the ulcer was the bleeding point.

Discovery of this lesion antemortem would hardly have modified the treatment in a way to have altered the outcome. Its discovery at autopsy, however, is evidence of the complexity of diagnosis in gastro-intestinal hemorrhage.

CONCLUDING REMARKS

This group of 7 cases taken as they came, all within the months of October and November, 1937, on one general medical ward of twenty beds, emphasized for my colleagues and myself certain points which we are glad to lay before the reader.

On the diagnostic side it becomes apparent that the determination of the source of upper gastro-intestinal tract hemorrhage is by no means always simple, and from symptoms and physical signs alone often impossible.

Patients with stories completely consistent with ulcer turn out to have gastritis (Cases II and IV) or cancer (Case I). Patients with stories highly suggestive of cancer of the stomach turn out to have benign ulcer and gastritis (Case VI). In a case of obvious cirrhosis of the liver with bleeding, it turns out that the bleeding is from an ulcer, not from varices (Case VII). That gastritis may be a cause of major hemorrhage from the stomach is a point worthy of emphasis.

The moral to be derived from such facts is, of course, that it is necessary to study any patient with upper gastro-intestinal hemorrhage by every available means that his condition permits until a diagnosis has been established. Barium examinations can be made without undue risk even when hemorrhage is continuing if special precautions are observed. We are making such examinations earlier than we did a few years ago.

The x-ray examination should include in all cases careful search for esophageal varices. Their demonstration by roentgenography is a comparatively recent advance and is very important. It is to be noted that none were found in Case VII. That fact perhaps should have made us suspect that some other lesion was responsible for the hemorrhage.

Gastroscopy is a very important aid to diagnosis. The introduction of the flexible gastroscope constitutes an important diagnostic advance. The diagnosis of gastritis and that lesion as a source of bleeding may often be established in no other way. When ulcerations are present the gastroscopist may be able to determine by inspection with a high degree of accuracy whether they are benign or malignant.

On the therapeutic side the points I should like to stress as of especial present-day significance are, first, that slow drip

transfusions of citrated blood can be given with very little risk of aggravating hemorrhage and constitute an extremely important procedure in upper gastro-intestinal hemorrhage; and, second, that it is probably safe and desirable to begin feeding in bleeding gastric cases much earlier than is generally customary. We are following Meulengracht, part way at least, in this matter.

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BACK PAIN IN GASTRO-INTESTINAL DISEASE

IN most instances a complaint of pain in the back at any level automatically suggests the advisability of considering disease of the vertebral column, either functional or organic in nature. Such an explanation is the obvious one, and until vertebral column or spinal cord disease has been ruled out, further search for an explanation of the presenting symptom is not indicated.

There are certain individuals, however, who have back pain as a presenting symptom but in whom a careful search reveals no evidence of postural defects or disease of the vertebrae or of the central nervous system. Under such circumstances, it is of the utmost importance to recognize the fact that not infrequently disturbances of the gastro-intestinal tract may be associated with symptoms that are predominantly, or at times entirely, localized in the back. Since the time of Mackenzie it has been recognized that patients suffering from digestive tract disease may have back symptoms. This point has rarely been stressed, however, and only rarely does one find reference to the fact that back pain may be the only symptom.

Too frequently lumbosacral pains are blamed on hypothetical absorption of toxic products from the digestive tract, and the patient is told that he has a toxic arthritis due to intestinal absorption. Such a statement is usually an incorrect one, and it is yet to be proved that joint symptoms are indeed the result of absorption of intestinal poisons. That constipation not infrequently is associated with low backache is true, and relief of constipation not infrequently influences favorably the patient's symptoms. It is probable, however, that

any fulness of the sigmoid or lower colon may, by mechanical action alone, cause the back symptoms, and this has been suggested by the work of Alvarez and others.

Over a period of years we have had occasion at the Massachusetts General Hospital to study the pain produced by distention of the digestive tract at various levels. On numerous occasions back pain has been reproduced simply by distention of a balloon in one or another portion of the gastro-intestinal tract, and on a few occasions back pain has been the only symptom thus produced. Relief has always followed as soon as the distention of the local segment has been released.

Based on the work of various experimenters, including our own, we have come to the conclusion that almost all, if not all, symptoms caused by disturbances of the digestive tract are fundamentally associated with the local production of distention either above an area of spasm or above an area of organic disease with actual constriction. Because of the frequency with which back pain has been reproduced experimentally, we have been particularly interested in this symptom in relation to organic and functional disease. The following cases will serve to illustrate the importance of a proper evaluation of back pain and its occasional occurrence on the basis of disease of the gastro-intestinal tract.

Case I.—The patient was a young woman of thirty-three years, whose admission complaints were *epigastric* distress associated with severe *middorsal pain* of three weeks' duration. Her past history included a story of pneumonia at six years and acute nephritis at the age of eighteen. Numerous sore throats eventually required a tonsillectomy at the age of twenty, and the following year a dilatation and curettage was done for hypertrophic endometritis. Five years prior to being seen for her present complaint she had had an acute gastro-intestinal upset of three weeks' duration, associated with epigastric distress. x-Rays at that time were essentially negative except for some evidence of irritation of the stomach. Two years later she had an acute attack of right lower quadrant pain, which resulted in an abdominal exploration with a diagnosis of acute salpingitis. During her training as a nurse fifteen years prior to her present illness she had had scarlet fever and repeated attacks of joint pain, which with the sore

throats had been the cause for the tonsillectomy. There had been no subsequent joint symptoms.

Her present illness was of three weeks' duration and followed a period of extreme fatigue while taking care of a difficult patient. At this time she noted *epigastric distress*, relieved by food and soda. *As the symptoms progressed the epigastric pain became less marked and was associated with, and at times replaced by, a very severe pain located in the mid-dorsal region at about the level of the tenth dorsal vertebra.* This back pain at times was the only symptom. It was sufficient at times to awaken her at night. The back pain was always relieved by milk of magnesia or other alkalis.

Physical examination was essentially negative except for slight spinal tenderness to deep pressure at the level of the tenth dorsal vertebra, without any limitation of spinal motion. Examination of the abdomen was negative.

All laboratory data were negative, and a diagnosis was made of penetrating duodenal ulcer, which was thought to be on the posterior wall of the duodenum.

A gastro-intestinal series was reported as follows: "The esophagus is normal. The mucosa of the stomach is markedly thickened, and there are some secretions. The stomach empties rapidly, and there is overdistention of the small bowel. The mucosa of the small bowel appears thickened throughout. A definite ulcer crater is seen on the *anterior* wall of the first portion of the duodenum. This crater is about 1 centimeter in diameter and about 1 centimeter in depth. At 24 hours barium is scattered from the cecum to the rectum. The small bowel is empty. Conclusions: There is definite evidence of an active duodenal ulcer, gastroduodenitis and abnormal emptying of the stomach."

A simple régime which provided adequate rest combined with the usual dietary and medicinal treatment for ulcer relieved all of the patient's symptoms in the course of about ten days.

Comment.—This case is of interest because of the severity of the back pain in relation to anterior wall duodenal ulcer. The diagnosis was relatively simple because of the periodicity of the pain and its relief by food and alkali. The unusual feature was the severity of the dorsal pain, which for the

greater part of the present illness was the only symptom, replacing almost completely the usual epigastric pain.

Case II.—This patient was a graduate student of twenty-four years, who consulted me because of low dorsal back pain, associated with fatigue. His past history was absolutely irrelevant, with the exception of an attack of acute appendicitis previously, for which he was successfully operated upon. His habits were noncontributory.

His present illness was of six months' duration and consisted in rather severe pain, fairly well *localized just to the left of the tenth dorsal vertebra and not radiating*. It came on in the middle of the afternoon and was severe enough to interfere with strenuous physical exercise. As a matter of fact, he had consulted a physician for relief of this pain, and had been told to discontinue crew work at the institution where he was pursuing his studies. Orthopedic studies were carried out, and for some time, although all the findings were negative, it was considered that the back pain was due to a local spinal condition. It was noted that the only aggravating factor was fatigue, and it was felt that the pain was probably on a postural basis inasmuch as x-ray studies failed to show any evidence of spinal disease.

Because of the persistence of his symptoms in spite of the usual orthopedic measures, the patient consulted an internist, who reviewed the entire situation carefully and concluded that his back pain was not due to bone or nerve disease. Close questioning at that time elicited no further facts except as above stated. Because all routine studies, including physical and laboratory examinations, were negative, it was decided to repeat the x-ray studies of the spine and to make a gastrointestinal examination. Roentgenologic examination of the entire spine revealed no abnormalities except rudimentary twelfth ribs. A barium meal showed a small diverticulum-like area over the lesser curvature side of the duodenum compatible with ulcer. This was associated with vigorous peristalsis on two observations. Following complete atropinization the latter x-rays were repeated and were reported as follows: "There is evidence of what I believe to be a definite ulcer of the duodenum with a diverticulum in both the lesser and greater curvature of the cap."

There seemed no reason to doubt the diagnosis of duodenal ulcer, and a simple ulcer routine was immediately instituted with complete relief of the back pain. Further questioning revealed the fact that at times the patient had been conscious of very mild indigestion at the time he had back pain. It was so slight as to make the patient neglect to mention it to the physician until pointed questions were asked. He also recalled the fact that after strenuous tennis or extreme physical activity he had been awakened at night between 12 and 2 o'clock with back pain, in this case undoubtedly due to his duodenal ulcer.

Since the establishment of the diagnosis, routine ulcer therapy has been completely successful in handling the patient's symptoms.

Comment.—This case is of particular interest inasmuch as the dorsal pain of which the patient complained was associated with strenuous physical activity. The digestive symptoms were so slight as to be completely overlooked by the patient, and for a long time the attention of the patient and that of his physician was directed toward the relief of what was considered a "back condition." Only by a process of elimination was the correct diagnosis established.

Case III.—This fifty-year-old salesman entered the hospital on the orthopedic service for study of symptoms supposedly referable to the dorsal spine. His past history was absolutely irrelevant.

Present Illness.—The patient was well until seven months before admission, when he became aware of pain which radiated from the midepigastrium around the right side of the chest into his dorsal spine. This pain occurred following a mild attack of "grippe," but was not affected by respiration, cough, or bodily movements. It was completely relieved by a few manipulations by his local osteopath.

Four weeks before admission the patient slept in a boat and struck his head on the coaming. He did not notice pain until several days after the accident, at which time he became conscious of a *pain which radiated from the right interscapular region, around the ribs and anteriorly to the sternum.* It was not related to food, exercise or movements. It was worse when he became fatigued. Osteopathic treatment gave no relief.

On the night of entry he was awakened by severe pain in the region of the lower sternum, which subsequently disappeared. The only other point of importance is that he had always complained of slight superficial tenderness over his sternum for many years. This tenderness was not related in his mind to anything in particular.

Physical examination was essentially negative except for very slight superficial tenderness over the xiphoid process to moderate pressure. There was no tenderness in the back, no limitation of motion in the dorsal spine, and no pain on motion of back or scapula. The *pain was localized to the right of the fifth and sixth dorsal spinous processes*, and on admission it was felt that there was a possible dorsal spine strain with pressure on the fifth and sixth dorsal roots. A neurologic examination was absolutely negative.

Laboratory data showed a red blood count of 4,630,000, with a hemoglobin of 80 per cent and a white blood count of 10,000 to 12,000. There was a normal differential and blood smear. Urine examination showed a concentrated urine with a specific gravity of 1.024 to 1.030, but was otherwise negative except for an occasional white cell in the smear and a rare hyaline cast. The blood Hinton was negative. All studies on the spinal fluid were normal, and the sedimentation rate was within normal limits.

A medical consultant examined the patient and expressed the opinion that gallbladder and gastro-intestinal x-ray studies should be made, but at the same time said he doubted the presence of any positive disease in the digestive tract.

In a consultation with one of the neurologic surgeons, Dr. Reginald Smithwick, to whom I am indebted for this history, the latter agreed definitely with the possibility of a posterior wall duodenal ulcer, but could make no such diagnosis from the history. He felt that there was no spinal disease but that complete neurologic studies were indicated.

x-Rays of the chest were essentially negative. A cholecystograph showed slight diminution of the density of the gallbladder from the dye, but was otherwise negative. A gastro-intestinal series showed a deformity of the duodenal cap with a large ulcer crater on the posterior wall near the apex of the cap.

Because of the latter finding, the patient was transferred from the orthopedic service to the surgical service, and an operation was performed by Dr. Smithwick. On exploration of the abdomen, a large ulcer was found in the second portion of the duodenum, penetrating into the pancreas. The ulcer was about $1\frac{1}{2}$ cm. in diameter, going essentially through all layers of the duodenum into the pancreas. There was diffuse inflammation and edema of the pancreas around the ulcer. Because of the difficulty of attempting a local excision, a subtotal gastric resection was performed.

Convalescence was uneventful, and the back pain of which the patient had complained completely disappeared. During the past fourteen months there has been no recurrence of the patient's presenting symptom.

Comment.—This case is of interest because a duodenal ulcer was suspected as one of the possible causes for his dorsal pain, but it was impossible to obtain, even after close questioning, any history suggestive of a peptic ulcer.

Case IV.—This patient was a sixty-three-year-old physician,¹ who entered the hospital on the neuropsychiatric service with a diagnosis of intercostal neuralgia. His complaint was that of *posterior midthoracic pain, radiating to the lower costal border and under the sternum*, for a period of sixteen years. This pain was increased by nervous tension or fatigue and never radiated to either shoulder. On one occasion it seemed to travel up the neck to the angle of the jaw.

Seven years before admission, he began to note that undue exercise, fatigue, constipation and posture might bring on the attacks, and at this time he was unable to sleep on his left side. The reference of the pain was the same, but the severity increased even to the point of vomiting. x-Ray studies were taken of the spine, stomach and bowel, and these showed nothing but so-called "minimal hypertrophic arthritis." At times the pain was severe enough to warrant the use of morphine.

During the three to four months preceding admission he had constant *pain between the shoulders at the inferior angle of the scapula*, and had had acute attacks precipitated by the factors already mentioned, with radiation to the substernal

¹ This patient was seen in consultation with Dr. Reginald Smithwick and Dr. W. Jason Mixer.

region. These were unrelieved by vomiting, and relieved only by morphine. They came on every three weeks and lasted several days. At the time of admission the patient *localized his pain more on the right side along the eighth intercostal space.*

The family history and past history were irrelevant. The patient had lived an extremely active life, for the most part, in the practice of his profession.

Physical examination showed rather poor posture, with no other outstanding findings. There was a slight cardiac enlargement with a blood pressure of 190/115. There was a moderate systolic murmur at the apex, and the aortic second sound was accentuated. There was a questionable diastolic murmur at the left sternal border. A neurologic examination was absolutely negative.

The patient was seen by a neurologic consultant, who was unable to make a diagnosis of disease of the nervous system. A cardiac consultant felt that there was hypertensive and arteriosclerotic heart disease, but did not think this contributed to his symptoms.

x-Ray examinations of the heart and lungs were negative except for slight prominence in the region of the left ventricle and tortuosity of the aorta, without evidence of dilatation. Films of the spine revealed some spur formation on the lateral and anterior margins of the bodies of the vertebrae, and considerable sharpening of the articular margins between the ribs and vertebral column, characteristic of hypertrophic arthritis. A Graham test was negative. A lumbar puncture showed normal spinal fluid, and a lipiodol injection into the lumbar canal showed no evidence of disease. A gastro-intestinal series showed slight prominence of the gastric rugae, increased peristalsis and gross deformity of the duodenal cap, characteristic of ulcer; there was a small hiatus hernia.

Following these x-rays a medical consultant gave the following opinion: "From the story that I can obtain, it seems to me that fatigue, involving posture or strain on the dorsal region, quick changes in position, etc., are the factors producing the attacks. Duodenal ulcer may be present, but I cannot work out its relationship to his pain. I suggest the elimination

namely, further neurologic studies, including therapeutic novocain block during an attack."

Routine laboratory data were absolutely negative. The urine showed a specific gravity of 1.018, albumin +, with an occasional hyaline cast and occasional white blood cell and epithelial cell. The red blood count was 4,970,000; white blood count, 7300; hemoglobin, 95 per cent; and the differential count was normal. A Hinton examination was negative. An electrocardiogram showed slight right axis deviation, a late inversion of T₁ and a flat T₂. Studies of the spinal fluid showed normal dynamics, no cells, a total protein of 77 mg./100 cc., a negative Wassermann and a gold sol of 0112232100.

Following a rather prolonged observation, it was finally decided that it was impossible to explain the patient's symptoms on the basis of spinal or cord disease, and a diagnosis of duodenal ulcer was made on the basis of the x-ray findings. The patient was so advised, but he refused to accept such a diagnosis, and eventually it was necessary to attempt relief of his symptoms by a paravertebral block. This was done by Dr. Smithwick, who injected with alcohol the *paravertebral area at the level of the fifth, sixth and seventh dorsal vertebrae*.

From this time on the patient had no further pain and led an unrestricted life, as far as activity and diet were concerned. Six weeks later, however, his son reported that he had just had a profuse gastric hemorrhage. This attack was extremely severe, and the patient only gradually recovered. When he was strong enough to return to the hospital a further x-ray study was made of the gastro-intestinal tract, which revealed at this time a definite ulcer crater on the posterior wall of the duodenum, with a large area of edema around it.

Following the hematemesis and the positive x-ray findings the patient was convinced of the activity of his ulcer and immediately went on a strict ulcer régime for several months. Finally there appeared a new symptom of severe substernal oppression on effort. This gradually increased in intensity and eventually terminated in a characteristic attack of coronary thrombosis, from which he died.

Comment.—This case is of unusual interest because of the extreme severity of the low dorsal pain, simulating in every way disease at the level of the eighth dorsal vertebra. Numer-

ous consultants were confused as to the cause of his symptoms, and it was only by a process of elimination that a correct diagnosis was eventually obtained. Because of the atypicality of his symptom, the patient himself refused to accept the diagnosis of ulcer as the cause of his difficulties, followed out no instructions, and probably as a result precipitated further ulcer activity, which resulted in a serious hemorrhage. The subsequent development of symptoms of coronary heart disease is of only secondary importance inasmuch as these symptoms were entirely different from those originally complained of by the patient, were entirely limited to the substernal region, and did not alter the correctness of the previous diagnosis.

Case V.—This salesman of forty-eight years entered the hospital complaining of ten years of gastro-intestinal symptoms, consisting of flatulence, left lower abdominal discomfort, rumbling and, at times, lower abdominal tenderness and spasm. His past history was irrelevant.

The attacks of lower abdominal discomfort and left lower quadrant tenderness were characteristic of so-called "mucous colitis." They always followed emotional disturbances or prolonged fatigue, and were associated with loose mushy stools or extremely constipated bowel movements, accompanied by large amounts of thick tenacious mucus. In addition, there was a complaint of *back pain localized over the right and left lumbosacral region*, but particularly on the left. It was apt to occur during an attack of "colitis" and might persist for several days. It was dull in character, and relief appeared to be associated with a return of normal bowel movements. The relationship between bowel activity and the occurrence of lumbosacral pain had led to a diagnosis of lumbosacral arthritis due to intestinal absorption. At different times a very detailed dietary régime had been outlined, including the administration of lactic acid bacilli in order to combat intestinal putrefaction.

Over a period of several years he had received rather intensive treatment at the hands of orthopedic surgeons for his arthritis. The treatment consisted largely in the management of diet, bowel activity, and proper exercises.

On admission to the hospital his physical examination was essentially negative, except for a palpable sigmoid, which was slightly tender to deep pressure. A sigmoidoscopy revealed a

spastic, injected rectosigmoid, which was somewhat granular in spots with one or two points of capillary bleeding following sponging of the mucous membrane. The appearance was absolutely characteristic of the findings in "mucous colitis."

Examination of the blood, urine and stools was negative with the exception that there was a very obvious tendency to starch fermentation, evidenced by the stool studies. An x-ray examination of his spine revealed no definite abnormality of the lumbosacral and sacro-iliac regions, and a barium enema revealed no evidence of disease, but there was a moderate degree of spasm in the sigmoid and descending colon.

While in the hospital the patient complained from time to time of lumbosacral pain, and it was noted that this was relieved by a cleansing enema. It was of particular interest to note that *relief from the back pain was obtained in a few minutes after evacuation of the bowel*. The relief was so striking and it occurred so rapidly that the patient was given a bland solution by rectum to be retained. When the colon was filled he complained again of back pain, which subsequently disappeared as soon as the solution was evacuated. Subsequently, on numerous occasions it was noted that immediate relief was always obtained by evacuation of the bowel and that at times, even in the absence of bowel movements, adequate doses of belladonna would also provide relief.

Comment.—This case is of particular interest because of the fact that the patient had been diagnosed and treated for some time as if he had a case of lumbosacral arthritis, due to intestinal intoxication. Such a diagnosis, as a rule, represents rather faulty reasoning, although it is true that at times arthritis is benefited by improving the bowel hygiene. In this particular instance, the back pain was undoubtedly due to a full sigmoid with more or less marked local spasm. The rapidity with which relief was obtained by enemata quite obviously proved that emptying the bowel mechanically relieved the cause of the symptoms and that absorption of toxic products had nothing to do with the patient's so-called "arthritis." A more careful interpretation of the patient's history would undoubtedly have revealed the fact that the back pain was intestinal in origin and in no sense due to arthritis, and pro-

longed and rather unnecessary treatment would have been avoided.

Discussion.—The usual reference of pain from the gastro-intestinal tract is well known to be located in the midline anteriorly. This is amply supported by both clinical and experimental evidence. Gastroduodenal pain is almost always sharply localized in the midepigastrium, and colonic pain is nearly always localized in the hypogastrium, more or less near the midline, except when associated with disease of the colonic flexures.

Back pain as the only symptom or as the predominating symptom is rarely considered as being due to disease of the gastro-intestinal tract. Such a point of view is obviously a correct one, but the preceding cases, as well as experimental evidence, show that at times it is of the utmost importance to recognize the fact that this symptom may be due to digestive tract lesions. Recognition of this fact will result in a more nearly correct interpretation of the history, and at times will obviate many therapeutic difficulties.

CLINIC OF DR. JOE VINCENT MEIGS

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VAGINITIS, VULVITIS, AND CERVICITIS

Introduction.—This paper is a discussion of the various causes for leukorrhea or vaginal discharges which now occupy the attention of gynecologists everywhere. A great deal is known about them but there is yet a good deal more to learn concerning their actual etiology and their treatment. Marked progress has been made of late, and an endeavor will be made to present the new advances as well as the satisfactory types of older treatments.

Many patients come to the gynecologists complaining of a vaginal discharge, itching, and a disagreeable feeling in the vulva. There are numerous causes for these, and the investigation of the individual patient must be carried out with nearly all the possible reasons in mind. There are no characteristic symptoms, gonorrhea having the same sort of symptoms as a trichomonas or monilia infestation and all causing the same sort of local difficulty. Occasionally from the appearance of the discharge, or the odor from it, a tentative diagnosis can be made, but it must always be supported by a complete investigation. Discharges and irritations can be of various types, such as infection; infestation with parasites or yeasts; or unknown bacterial invaders, such as cause lymphogranuloma inguinale and esthiomene. The reasons for senile vaginitis, kraurosis, and leukoplakic vulvitis are probably hormonal and should be placed in another category.

Gonorrhea.—First of the infections involving the vagina, vulva, cervix, and the numerous small glands in these regions let us take up gonorrhea. There is no need for discussing the method of infection of this disease. There are certain things about the local lesions, however, that should be expressed. Gonorrhea usually affects the urethra, Skene's glands, Bartho-

lin's glands, and the endocervix before it extends through the uterine canal into the pelvis. The local disease is usually self-limited in the cervix and the various glands of the vagina and urethra, the duration rarely being over three months without any form of treatment. A persistent discharge following the original infection is practically always due to secondary invaders; it is rare indeed that a gonorrheal infection persists. Microscopic slides of smears are usually negative at the end of six weeks. At the end of three months it will probably be found that in almost every instance the gonococcus has vanished, unless reinfected.

A vaginal discharge originating in the cervix may be due to an acute gonorrheal infection or to a later infection by secondary invaders. Most chronic cervical discharges are due to the infection of a so-called "congenital erosion," or secondary infection following a gonorrheal infection, or as is most common, to infection of the exposed endocervical glandular epithelium following a laceration due to childbirth. The treatment of these lesions should be directed toward eliminating the exposed endocervical tissue. This may be accomplished by any form of cauterization, or by repair or amputation of the cervix. Local topical applications are of very little curative value. In deep-seated infections of the cervix and endocervix heavy cauterization may be considered but this type of treatment only checks the infection in the areas cauterized. To relieve this type of infection it is often necessary to resort to high amputation or even total hysterectomy. Local treatment such as light cauterization will care for superficial infections when the infection is limited to the exposed tissue or the exposed endocervical glands of the "congenital erosion." Cure can be accomplished only by complete removal of the entire infected area.

The theory of the retention of the gonococcus in the Skene's glands and Bartholin's glands is being discarded, and persistent infections are now considered to be reinfections from the same or another source: the infection going from the male to the female, from the female back to the male, being passed about by sexual intercourse. This happens in spite of the fact that it may be denied by the patient. The diagnosis of a gonorrheal infection in a woman, except in the first few weeks

is extremely difficult and complete reliance cannot be placed upon smears showing gram-negative intracellular diplococci. The only accurate method of diagnosis is a culture of the organism on special media that are obtained fresh from the bacteriologist and taken back to him at once for incubation. The time-honored three consecutive negative smear method is now unsatisfactory and a culture should be taken and repeated before a patient can be given a clean bill of health. The treatment should be general—cleanliness, rest in bed, and no dissipation of any kind—food or drink. Pitcher douches of salt solution or dilute potassium permanganate poured over the vulva are excellent. With a gentle swabbing out of the vagina and a cleansing of the cervix of its discharges to allow better drainage, the infection, if it does not go higher, rapidly subsides. Nowadays sulfanilamide is recommended highly; this should be given in doses large enough to kill the organisms. Eighty grains or more per day in the average adult female is about the proper dosage. It can be decreased or increased, depending upon the resistance of the patient, her size, her weight, and her blood studies. Heat treatment is extremely valuable—the patient being placed in an electrically heated chamber, the temperature being raised to a point high enough to destroy the gonococcus. After two or three such treatments it is usual for the gonococcus to disappear from the vaginal and cervical smears. There is no doubt that gonorrhea can be overtreated, and it is probable that rest in bed, or at least rest at home, absolute cleanliness, vaginal hygiene, and the use of sulfanilamide will take care of most cases. In some instances Skene's and Bartholin's glands are involved and must be opened. Skene's glands can be cauterized in the office under local anesthesia with the endothermy machine; and Bartholin's glands, if they become swollen and abscessed, can be drained by wide incision through the skin of the vulva. If the infection subsides and later a Bartholin's cyst is formed, this can be either dissected out or a silk suture can be sutured through it from skin to vagina, the thread being tied and left to allow proper drainage through the two small holes. The persistence of a gonorrheal infection in these areas is not a common condition.

The treatment of infantile or juvenile vulvovaginitis of

gonorrheal origin is best carried out by means of the female sex hormone estrin. This in proper dosage, and carried out long enough, will change the child's alkaline transitional epithelium of the vagina into the acid squamous type of epithelium of the menstruating woman. The vagina of the adult resists gonorrheal infection so it is logical to change the epithelium of the child into adult type. There is no danger in this treatment, although occasionally swelling of the breasts and even slight vaginal bleeding occur.

Chancroid.—The next infection to occupy our attention is chancroid. This lesion is much more uncommon than it was formerly and is not frequently seen in the various outpatient clinics dealing with the venereal diseases. It is caused by Ducrey's bacillus, and multiple small ulcers are formed on the vagina or the vulva, or even out upon the buttocks. Its cure depends upon cleanliness and painting the surface of the ulcers with pure carbolic or chromic acid. Frequently chancroid is accompanied by "buboes" or an infection of the lymphatic nodes in the inguinal regions and for these heat, to localize the lesion, and incision and drainage are occasionally necessary.

Tuberculosis of the vagina is rare and is usually an accompaniment of a tuberculous infection elsewhere, probably in the lung. It may possibly be a local lesion arising in the vagina itself. Not many instances of such infections have been reported. Treatment should be the same as the treatment of tuberculosis of any type—rest and hygiene.

Syphilis usually occurs in the form of hard chancre, an indurated, small ulcerated area either on the fourchette, labia minus, cervix, or near the urethra. This infection is often accompanied by hard lymph nodes in the groin. The treatment is of course the same as treatment for syphilis in any region. In a later stage it is possible to have the flat condyloma so characteristic of a second degree syphilitic infection.

Diphtheria is an infection occasionally found in the vagina, and usually is an accompaniment of diphtheria of the respiratory tract. Its cure should be that of diphtheria in any form—the use of the proper antitoxin.

Vincent's infection is extremely painful and tender and is accompanied by a very irritable discharge. It is cured

terized by a small red or grayish ulceration in the vagina. Smears show the presence of fusiform bacilli and spirilla. Treatment consists of neoarsphenamine given intravenously and painted locally upon the various small areas involved.

Lymphogranuloma inguinale, the so-called *third venereal disease*, is characterized by numerous ulcerating lesions in the vagina and the swelling of the lymph nodes in the femoral, inguinal, and iliac regions. It is oftentimes accompanied by a lesion of the rectum with hard induration and beginning stricture formation. The Frei test usually determines the diagnosis when the vaginal lesion reveals no definite organism that can be attributed to any other infection.

Esthiomene is a later development of this peculiar venereal infection and is now considered as a form of lymphogranuloma inguinale. Its treatment is difficult and wide excision of the lesion with the endothermy current is the best form of treatment. There is no specific therapy for this lesion.

Of the infections of the vagina, cervix, and vulva, gonorrhea is by far the most important, but it is necessary to bear the others in mind in order to carry out the proper treatment. Their diagnosis is very important and an accurate diagnosis can be made only by properly carried out bacteriologic investigation.

The next group to be considered are those of the infestations, due to either the trichomonas or yeast. **Trichomonas vaginalis vaginitis** is of the greatest importance. The literature of the past few years contains ten times as many articles on trichomonas as on other infection of these particular regions. It is probably present in from 16 to 17 per cent of nonpregnant women complaining of a discharge and in from 20 to 25 per cent of the gravid women. In some patients the organism is present without giving symptoms but under certain circumstances of lowered vitality, etc., this organism causes symptoms of a very disagreeable type. Most patients with leukorrhea who have been treated by other physicians without success, or who have been cauterized without success, have this particular infection. The clinical history is very typical; the patient complains of a burning, irritating, disagreeable vaginal discharge with a very pungent odor. Usually when the patient comes to the physician in his office she

ways been stated that one should make the diagnosis by looking at a hanging drop preparation after having diluted a drop of pus with warm saline. This is entirely unnecessary. On opening the vagina with a Graves' speculum, a small bit of pus is obtained and placed on a slide and a drop of warm water put on it. A cover slip is then placed on this and it is put under the microscope and looked at under a high, dry power with the light turned about halfway down. It is then very easy to see the small organisms twisting and jerking in all directions through the smear. Their size is often that of pus cells and sometimes they are confused with phagocytizing cells containing many bacteria that appear to be moving. If these are watched carefully it is found that only the inside is moving and that there is no motion to the cell itself. The diagnosis is not at all difficult if one accustoms oneself to looking for these organisms carefully in a moist smear of every discharge. Cultures are possible and have frequently been done, but it is not necessary to do so in most instances because the organism can be so easily seen.

The symptoms are those of an irritating, odorous discharge, the odor being very pungent and acrid and very typical. The patients have itching and burning, and a disagreeable feeling in the vulva. Sometimes the vulva is chafed, and there is chafing on the legs. Occasionally cases have been reported with abdominal pain and temperature, as though some inflammatory process were present; this may easily be due to the fact that there is absorption through the vagina into the pelvis with a swelling of the lymph nodes in the retroperitoneal tissues. The cervix itself is practically never involved. Frequently there is an accompanying urgency of urination, dyspareunia, and general complete unhappiness. That the trichomonas is specifically responsible for the discharge, discounting the presence of the streptococcus, which is nearly always present, has been proved by various authors who have planted the trichomonas in pure culture in the vagina of women without symptoms as the women who originally had the infection from which the organisms were obtained. This method of determination should not be repeated, but it has been done and is reported in various articles in the literature.

has taken a douche or attempted to clean herself as carefully as possible before his examination. It is then practically impossible to make an accurate diagnosis because any sort of treatment, even a simple water douche, will cause the trichomonas to vanish for a short length of time. Therefore, the diagnosis of this condition on the first office examination when the patient has recently (either the day before or the day of the examination) taken a douche is practically impossible. It is necessary then to wait until the discharge is again aggravated and have the patient report at her worst. The *Trichomonas vaginalis* is probably the organism that causes the vaginal infection, but it is probable that the trichomonas of the mouth and of the rectum can cause the same symptoms. There is much dispute concerning this. It may be that the trichomonas is the same whether it is in the mouth, the rectum, or in the vagina. Perhaps it changes from one type to another, depending upon its locality. The possibility of a vaginal infection due to improper hygiene in the region of the anus, perineum, and vagina is very great. The infection can be acquired from toilets, linens, towels, and I have had patients reporting with this condition who have lived with women known to have the infection. Frequently nurses who have taken care of patients who have it find themselves infected also. There is no doubt but what it is transferable and contagious, but in most instances its onset probably comes from a sweeping of fecal particles into the vagina by the incorrect method of wiping the anus from back to front, rather than from front to back. Women perform this feat incorrectly because they go to the toilet with their corsets on and are unable to wipe in the proper direction. The teaching of the correct procedure to younger girls and children is extremely important. Trichomonas vaginitis is most commonly found in young adults but it occurs in children and old women. It used to be considered unlikely that children would have this infection but lately there have been reports of little girls of from three years to the age of puberty being infected. The majority of cases are among those of the menstruating age but numerous ones are seen in patients past the menopause.

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Many methods have been advised describing how this disagreeable infection should be cared for. That no one treatment is satisfactory will be shown by the numerous methods that have been advised. Any treatment may give complete relief quickly, but the infection may come back. It is possible that the bladder may harbor the organism, and numerous reports have been made of urine specimens containing the trichomonas. Nothing but a carefully taken catheter specimen should be accepted as proof of this infestation but it is true that in some reports as many as 10 per cent of cases seem to have it. It is frequently noted that after a patient has been cleared of the disease as far as possible the infection comes back again, in spite of the treatment which has cured other patients. This may be due to infection from the male. There are conflicting reports concerning the infection of the male with this disease. Nevertheless in a recent résumé of the literature for this paper there are reports of at least 50 males who had it in the urethra, bladder, or in the prostate gland. This means that many more males than were suspected have this particular infection and that therefore if the treatment fails investigation of the husband should be undertaken to prove whether or not he is responsible for the recurrence of the disease.

The treatment of trichomonas vaginitis is enthusiastically described by every author, usually the form of treatment advised being the one in which the writer is particularly interested. It has been my experience to try practically every method of treatment advocated by these various writers, and I have found that it is very easy to clear up the local discharge and to make the patient comfortable. I have found that by continuously treating the patients they seem well. It has also been noticed on numerous occasions that following one or two treatments by any method the infection may disappear permanently. In others it has been noticed that in spite of the most carefully planned treatment the lesion reappears in spite of anything that can be done. I have had patients whom I have treated daily for six consecutive weeks without being able to clear the infection. It seems to me that it is probable that these persistent or recurrent infections are due either to infection of the female bladder or to infection in the husband

who reinfects the patient. It is most important, therefore, to find out whether or not there is any source of recontamination after a proper course of treatment has been given without cure. The first treatment should be carried out for one month, until the catamenia begins, then for about a week directly after the period. One should then wait to see whether or not there is a recurrence of the discharge before and after the next period. Some gynecologists prefer to continue to treat their patients after one month of careful office treatment before and after each period for about six months. The number of immediate favorable responses are so great, and so many of the recent articles speak of one to three months' "cures," that it is impossible to say how curable the disease is. I have found it extremely difficult to cure and tell my patients that I can make them comfortable, that I can rid them of their trouble by constant care and treatment in the office, but that I cannot guarantee that it will not return. It is very easy to relieve the patient of her symptoms but to cure the disease is extremely difficult. The tabulation shows the various vehicles advocated as treatment in the recent literature.

Quinine	Protargol
Arsenic	Mercurochrome
Lactic acid	Gentian violet
Picric acid	Acroflavine
Pyroligenous acid	Iodine
Silver picrate	Neoarsphenamine
Devegan	Lead acetate
Sodium perborate	Zinc oxide
Glucose	Metaphen
Salt, 25 per cent	Lassar's paste
Drying	Kaolin
Green soap	P carbamino phenyl arsenic acid
Bichloride of mercury	Silver nitrate, 20 per cent
Broth filtrates	

When a great number of treatments are advocated there is no question of there being a specific method of cure. The proper way is to first make the diagnosis, to gently and carefully clean out the vagina with dry cotton, and then to use any treatment that one wishes, doing it carefully and thoroughly as the directions prescribe in the various articles that are written upon it, and to carry this out for as long as six months.

In doing this the largest number of cures will be obtained. One must by trial and error find out which method is best suited to each individual. The question of reinfection from the male must not be overlooked.

Another interesting and not uncommon infestation of the vagina and vulva is by the yeast *monilia*, and occasionally the *leptothrix*. The *monilia* is the most common and it causes a vulvitis and vaginitis. The diagnosis is not difficult to make microscopically, the long mycelia with their buds being easily seen in a moist smear, just as in the diagnosis of trichomonas infection. The *monilia* can also be found by staining the smear with gentian violet. *Monilia* so frequently accompanies diabetes and pregnancy that if one can say the trichomonas is not present and responsible for the discharge *monilia* is. It is the cause of oral thrush in children who are born to parents having *monilia*. This fact has been proved by the transfer of the pus from the vagina of an infected mother to the throat of the child. Patients with *monilia* may have no symptoms whatsoever, but others have a very irritating, pungent, highly acid, flaky, and pussy or watery type of discharge as seen in *thrush*. The disease is worse before and after menstruation. Frequently when in patients with a pruritus thought due to diabetes who have been properly treated for their diabetes the itching, burning, and discharge continue, the *monilia* or yeast-like infection can be found. It is either an acute or chronic disease and can last for years. The treatment is simple and effective and consists of painting the region and washing out the vagina with 1 per cent watery solution of gentian violet.

Senile vaginitis, leukoplakic vulvitis and kraurosis are combinations of atrophy and infection. Senile vaginitis is not due to any specific organism known and is usually accompanied by an irritating discharge, and one will find that on observing the vagina there are many small punctate areas that appear to be small ulcerations. Smears of the discharge will show numerous pus cells, many bacteria, and many cells of the deeper layers of the epithelium of the vagina, the menopause cells. The mucous membrane of the vagina is broken down in small areas and is thin because of the atrophy of the epithelium that occurs at the climacteric. The underlying layers (transitional and basal) beneath the spinal or cornified layer are exposed

and the so-called "menopause cells" arise from these areas. Adhesions are frequently found due to the adherence of these small, red, ulcerated spots. Severe acute senile vaginitis is frequently accompanied by small filmy adhesions, and a chronic one by tough adhesions which are practically impossible to break up. Formerly the proper treatment of this condition was to paint the vagina with Churchill's iodine or full strength iodine under a light anesthetic in an endeavor to cause peeling of the upper layers of the epithelium and later healing.

Since our newer knowledge of the vaginal mucosa and its response to the female sex hormone, estrin, and since we know that we are able to change the transitional epithelium covering the vagina in a child by means of estrin to the adult type, it is reasonable by estrin treatment to endeavor to change the atrophied vaginal mucosa of the menopause into the adult mucosa of the menstruating woman. This is possible. After giving estrin in large and prolonged doses the mucosa changes from the thin atrophied mucous membrane to a thicker and healthier mucous membrane. When the vaginal smear is found to be made up of nothing but squamous and cornified epithelium with or without nuclei then the full effect of estrin has been obtained, then the discharge ceases. Two methods of giving estrin have been tried—orally and locally in the vagina. It is my impression that much more satisfactory results are obtained by using large doses of estrin in suppository form in the vagina.

Leukoplakia vulvitis and **kraurosis** are evidence of changes due to lack of the female sex hormone, and, just as in senile vaginitis, the vulval epithelium can be changed by the use of the female sex hormone. Thus it is possible in patients with leukoplakic vulvitis and kraurosis to give some relief by the use of this treatment. If, however, the kraurosis is advanced or the leukoplakic vulvitis is acute and severe this form of treatment is of no use and surgery must be resorted to. It is possible to think of leukoplakia of the vulva as the beginning of the change that ends in kraurosis; that is, in leukoplakic vulvitis there is a thickening of the superficial layers of the epithelium, the cornified layer being much thicker than the transitional or basal layer, and the underlying connective

tissue may be spongier due to edema and round-cell infiltration, whereas in kraurosis the epithelial layer has shrunk tremendously and the subcutaneous connective tissue, after the inflammatory process through which it has gone, is much thicker and contains great masses of collagen. In leukoplakic vulvitis large numbers of lymphocytes can be seen beneath the epithelial layer, denoting chronic inflammation. In kraurosis the lymphocytes are usually pushed down out of the way and are bunched together. The red vulva with white patches, the typical leukoplakia, is easy to differentiate from the smooth parchment-like vulva of kraurosis. Here the labia minora are obliterated, even the clitoris being buried sometimes in the parchment-like tissue. The treatment is either surgical or by means of estrin.

Besides the lesions described above there are other causes of vulval and vaginal difficulties such as allergic manifestations—eczemas, and skin changes due to food sensitization; there are mechanical causes for vaginitis such as strong contraceptives, scratching, the use of cotton or cellulose in the vagina or against the vulva during the menstrual period, or irritating discharges due to puerperal infection. There are leukorrheas and vulval irritations due to the discharge from a pyometrium or to retained products of conception. There are many others but the most common are those listed and described above. Treatment is not difficult providing the diagnosis is correctly made. Some of the treatments are specific, but others are not. *Trichomonas vaginalis* vaginitis is the most common and one of the most difficult to cure. We must not be led astray by what we read in the literature or in advertising pamphlets but must choose the treatment that we can best handle and carry that treatment out to its final conclusion.

CLINIC OF DRS. ASHTON GRAYBIEL AND PAUL D. WHITE

FROM THE CARDIAC CLINIC AND LABORATORY OF THE MASSACHUSETTS GENERAL HOSPITAL

CARDIAC FUNCTIONAL TESTS

AN estimation of the functional capacity of the heart should be included in every complete cardiac diagnosis. This is often possible, in the early stages of heart disease, by careful inquiry into the ability of the individual to perform work; the decrease in exercise tolerance is considered a measure of the degree of heart failure. The desirability of a more accurate method of determination has long been apparent and many tests have been devised in the attempt to measure quantitatively the functional capacity of the heart. It is our purpose here briefly to discuss the nature of such tests and to describe and criticize certain of them.

In testing the functional capacity of the heart it is a matter of importance that the full extent of its power be known. If signs and symptoms of heart failure are present with the body at rest, there is little or no cardiac reserve remaining as the heart is working at its full capacity. The problem becomes difficult, however, when the reserve power of the heart is considerable. In such instances the heart must be placed under a condition of strain before its power can be appreciated. Ideally this strain should involve the heart alone and should be sufficient to test its full ability. Practically this is impossible because in any work test structures other than the heart are also involved, and the response may be limited by the pulmonary capacity or by the general fitness of the individual rather than by the heart.

The most that can be expected of any functional test is that at any given time it will measure, accurately, the ability of the heart to do work. It is necessary to realize fully that

even this information is of a limited character. Functional tests must not be regarded as an answer to all doubtful cardiac problems but to the specific question as to how much work the heart is capable of performing. In many instances this information will prove misleading unless placed in its proper light according to the particular problem under consideration.

The methods of studying and testing cardiac insufficiency have undergone great development in recent years. Interest in examination in the nineteenth century was centered chiefly on such simple methods as auscultation and percussion and only toward the end of that century were introduced sphygmography and the measurement of the blood pressure. In recent years the development has continued at a rapid pace. Elaborate studies have been made of the quantitative relations of the circulation based on the science of hydrodynamics. Methods are now available for measuring the minute volume of blood flow, stroke volume, and circulation time. The physiology of respiration and the changes observed in heart disease have been exhaustively investigated. Many properties of the blood have been measured and studied by physicochemical methods. Electrocardiography has become a routine procedure. Roentgenography has found an important place and, quite recently, roentgenkymography has demonstrated important possibilities.

It is not feasible here to describe the many tests which have been proposed as aids in the determination of cardiac function. Nor is this desirable. Clinical medicine has shown little interest in the results of the great majority of such investigations and, for the most part, with good reason. Many of the tests require considerable apparatus and specialized technical training. Even in large clinics where apparatus, space, and technical assistance are available it is unusual to find elaborate cardiac functional tests routinely used. However, certain of the simpler tests have not found the favor they deserve. We are strongly of the opinion that this is largely due to an improper appreciation of their usefulness as well as of their limitations.

One of the most satisfactory tests available at this time is the step test as modified by Master.¹ It is simple yet meas-

ures quantitatively the amount of work performed. It takes into account the sex, age, and weight of the subject, but of course does not prove that cardiac weakness is the only explanation of a subnormal response; any factor causing ill health must be ruled out before the heart alone is to be incriminated. Adequate standards for normal individuals have been constructed. The method is as follows: After obtaining the resting blood pressure and pulse rate the patient walks over a small platform with two steps. Each step is 9 inches high so that one climb is $1\frac{1}{2}$ feet. The theoretically normal number of ascents is determined by reference to the table of standards and the patient makes these in one and one-half minutes. Two minutes after cessation of the exercise the blood pressure and pulse rate should have returned to the original level; 10 points' difference in the blood pressure or pulse rate is the extreme limit permitted. After determining the maximum number of ascents which will allow the blood pressure and pulse rate to return to the resting level in two minutes, the percentage of efficiency may be calculated by dividing this number by the normal number obtained from the standard tables. Precautions which must be observed before the test is performed are described by the author.

Another good test, although considerably more complicated, is the determination of oxygen consumption following a standard amount of work. Reference may be made to the recent articles by Nylin² and by Katz and his coworkers.³ This test is based upon the fact that patients with organic heart disease require a greater amount of oxygen to perform a given amount of work than do normal persons. The oxygen consumption is determined during rest and after a given grade of work. The increase in oxygen consumption is calculated as a percentage of the resting value and this increase has been found to vary within fairly narrow limits in healthy individuals and is independent of body weight, provided that the latter is within physiologic limits. In patients with considerable heart disease the increase in oxygen consumption is found to be consistently greater than in the normal. However, in the early grades of heart failure there is less consistency and the results are sometimes within the normal range. One of the most widely used tests is that proposed orig-

inally by Frost⁴ and later modified by others.⁵ It is based upon the physiologic fact that an increase in intrathoracic pressure produced by forcible expiration causes a rise in systolic blood pressure. By having the subject blow against a known resistance a strain is placed on the cardiovascular system. The resulting changes in arterial pressure, cardiac rate and rhythm are measured. This test with certain elaborations has been applied to many thousands of individuals and the users are convinced that it is a valuable test of cardiac efficiency.

An apparently valuable test which has, however, found little favor is the measurement of ventilation as proposed by Harrison and his coworkers.⁶ It is particularly fitting because it is based upon the cardinal symptom of heart failure, dyspnea. The pulmonary ventilation is determined during two minutes of standardized exercise and five minutes immediately afterward. Both are expressed in liters per square meter of body surface. Using the formula:

$$\text{Dyspnea} = \frac{\text{Ventilation}}{\text{Vital capacity}} \times \left[1 + \frac{\text{ideal weight} - \text{actual weight}}{2} \right]$$

it was found that this index is more or less independent of the nutritional state and relatively independent of age. It was further found that the ventilation index is usually normal in subjects with cardiac neurosis, slightly above normal in subjects with early organic heart disease and very much above normal in patients who have or who have had congestive failure.

Functional heart tests have been proposed in which electrocardiograms are taken before and after work. Reference may be made to recent articles by Heier,⁷ Katz and Landt,⁸ and Borgard.⁹ This test is especially designed to detect instances of coronary heart disease. It has been shown that exercise may cause significant electrocardiographic changes in patients with coronary heart disease and in elderly individuals in whom there is no clear evidence of heart disease. These changes are usually in the T waves or in the S-T segments but other abnormalities including various types of arrhythmias may occur.

Various tests have been proposed and described in which

x-ray studies of the heart are made before and after exercise or some modification of Mueller's and Valsalva's experiment. Of particular interest are the experiments of Nylin² who measured the heart volume under various conditions by taking synchronous exposures of the heart from the anteroposterior and lateral aspects using powerful x-ray tubes.

Studies in the volume or rate of blood flow have proved rather disappointing as methods of testing cardiac efficiency. The same may be said for Kauffmann's diuresis test, the response to low oxygen tensions, the simple estimation of vital capacity, breath holding, or venous pressure.

In many instances it is not feasible or desirable to subject the patient to any special test of heart function. This by no means excludes the possibility of its approximate estimation. Walking, climbing stairs, running, and various other types of exercise which are included in the routine of life provide good tests of heart function. It is simple and convenient to question a patient concerning the ease with which he normally accomplishes accustomed tasks and thereby gauge whether or not his ability to exercise has decreased. As Lewis¹⁰ points out, a comparison between the healthy and unhealthy states of the same subject is usually far more satisfactory than between a healthy and an unhealthy individual. Many times it is possible to trace quite accurately the gradually decreasing cardiac reserve in heart failure of both congestive and anginal type. White¹¹ has proposed a simple classification which is as follows:

1. Full normal activity possible without cardiac symptoms.
2. (a) Activity slightly restricted by symptoms.
(b) Activity moderately restricted by symptoms.
(c) Activity greatly restricted by symptoms.
3. No activity possible without symptoms.
4. Symptoms even at rest.

Another classification proposed by the American Heart Association¹² is as follows:

Functional Capacity

1. Patients with organic heart disease, able to carry on ordinary physical activity without discomfort.

2. Patients with organic heart disease, unable to carry on ordinary physical activity without discomfort.
 - (a) Activity slightly limited.
 - (b) Activity greatly limited.
3. Patients with organic heart disease and with symptoms or signs of heart failure when at rest, unable to carry on any physical activity without discomfort.

Possible Heart Disease

Patients who show abnormal signs or symptoms referable to the heart but in whom the diagnosis of heart disease is uncertain.

Potential Heart Disease

Patients without circulatory disease whom it is advisable to follow because of the presence or history of an etiologic factor which might cause heart disease.

As a result of our study of cardiac functional tests we have concluded that the chief difficulty lies not as much in the method as in the interpretation of results. An ideal test giving precise information would often be of small value in diagnosis, prognosis, or treatment. In order the better to emphasize this cardinal point the importance of functional tests will be considered in regard to some of the common types of heart disease.

Rheumatic Heart Disease.—A knowledge of the functional capacity of the heart may often prove of value in the diagnosis, treatment, and prognosis of this condition. In regard to diagnosis it has been shown that congestive heart failure in young individuals is invariably associated with activity of the rheumatic process. Thus in young individuals with greatly decreased heart reserve active infection should be suspected especially if this decrease seems out of proportion to the presenting physical signs.

In chronic rheumatic heart disease the cardiac reserve has been shown to offer a good guide to prognosis¹³; it also aids in treatment by revealing the amount of physical exercise allowable without strain. For example, A. G., a boy aged six-

teen years, came to the clinic because he was found to have "heart trouble." He had no complaints and was able, apparently, to equal his fellows in sports. Physical examination revealed no definite cardiac enlargement but there was evidence of definite disease of the mitral valve. The pulse rate resting was 76 a minute and the blood pressure was 112 mm. Hg systolic and 70 diastolic. The vital capacity was 2980 cc. On walking rapidly up and down a flight of stairs the blood pressure rose to 146/60 and the pulse rate to 88. Within three minutes the blood pressure was 110/68 and the pulse rate 76. Doubling the amount of exercise raised the blood pressure to 154/66 and the pulse rate to 88 but within three minutes both values were at the resting level. There was no doubt but that this boy's heart responded normally to exercise and there was likewise no hesitation in allowing him to engage in moderate exercise. Although his exercise tolerance is now as good as most normal individuals his age the prognosis is not, simply because of the possibility that he may have further cardiac damage within a relatively short time.

Another patient, A. D., a woman aged thirty-seven years, entered the hospital in congestive failure. She had had cardiac symptoms due to rheumatic heart disease for many years. Physical examination revealed a moderately enlarged heart with well-marked mitral stenosis and a slightly abnormal elevation of the blood pressure. Following routine hospital care she improved and was able to exercise a little. The pulse rate at rest was 76 and the blood pressure 158/86. The vital capacity was 2600 cc. A small amount of exercise, walking slowly up and down one flight of stairs, produced slight dyspnea and the blood pressure rose to 188/90 and the pulse rate to 112. These values gradually returned toward the initial level and after six minutes the blood pressure was 160/84 and the pulse rate 80. Actually this response was better than anticipated and encouraged the opinion that it would be safe to allow her a little activity and that the immediate prognosis was favorable.

Thus an accurate estimation of the functional heart reserve would be of value in most cases of chronic rheumatic heart disease. It forms a good guide to prognosis although, of course, it has to be qualified because of the possibility of com-

plications such as a return of active rheumatic infection, auricular fibrillation, or subacute bacterial endocarditis.

Subacute Bacterial Endocarditis.—This complication of heart disease offers an excellent opportunity to point out the limitation of functional heart tests. For example, a patient in the very early stages of subacute bacterial endocarditis and with minimal heart damage might well have a good heart reserve. In this case to argue that the prognosis is good because the cardiac reserve is good would be folly. It merely emphasizes the undesirability of interpreting such tests in a rule-of-thumb manner.

Luetic Heart Disease.—In luetic aortitis or even aneurysm of the aorta the decrease in functional capacity of the heart might be little or none. Even in the early stages of aortic regurgitation of luetic origin the reserve might be good. Despite a good heart reserve, however, the prognosis would be poor and it would be necessary to limit sharply the activity if there was danger of rupture of the aorta. How erroneous it would be to use the same standards one would in considering rheumatic heart disease! A patient with mitral stenosis and with much less heart reserve could safely be allowed more exercise and would have a better prognosis. On the other hand, when considering a group of patients with luetic heart disease, other things being similar, the better the exercise tolerance the better the prognosis.

Hypertensive Heart Disease.—Here, as in chronic rheumatic heart disease, a knowledge of the cardiac reserve will often be of value in prognosis and treatment. It may also be of value in determining when hypertension *per se* has produced hypertensive heart disease. As in other types of heart disease there is often considerable discrepancy between the symptomatology and the objective findings. Accurate knowledge of the functional capacity of the heart would be important in deciding in what measure to be influenced by the subjective or objective findings.

Neurocirculatory Asthenia.—There are a considerable number of individuals without any structural defect of the heart, and a large number of patients with slight grades of heart injury who have distressing cardiac symptoms. It is very important to be able to learn the true functional status

of the heart in such cases. In many instances this cannot be determined by inquiring regarding their exercise tolerance because of the abnormal ease with which symptoms are provoked. Functional tests based on pulse rate and blood pressure determinations are sometimes misleading because of the general instability of individuals in this group. An interesting observation was made by one of us (P. D. W.¹⁴) during a Marathon race. The winner of the 25-mile race had, at the start, the highest pulse rate among the various contestants examined, namely, 118, and at the finish it was 110. The pulse rate was actually faster before he started than after he had run the 25 miles.

Two examples will be given of patients complaining bitterly of cardiac symptoms without sufficient cause.

D. L., a young man aged twenty-six years, complained of undue dyspnea, palpitation, and fatiguability on exercise. Repeated examinations in a thorough manner failed to reveal any abnormality save, usually, a rapid heart rate. On one occasion he was asked to do a simple exercise test; he was obviously excited. The resting pulse rate was 120 a minute and the blood pressure 140/78. The vital capacity was 4180 cc. After walking rapidly up and down one flight of stairs he was slightly dyspneic and the blood pressure was 158/96 and the pulse rate 130. In three minutes the blood pressure was 140/80 and the pulse rate 120. Doubling the amount of exercise caused a slightly greater increase in blood pressure and pulse rate but these again returned to the initial level within three minutes. Going over the stairs five times, which was about his limit due to lack of training, raised the blood pressure to 168/92 and the pulse rate to 136; he was quite dyspneic and tired. After three minutes the blood pressure was 134/76 and the pulse rate 118 and thereafter fell still lower before returning to the initial level. In this case the symptoms suggested heart disease but this was not substantiated by any method of examination including the simple functional test described above.

J. Z., a man aged thirty-seven years, came to the clinic with a number of complaints among which were undue dyspnea, palpitation, and fatiguability on exercise. Repeated examinations revealed nothing more than slight essential hyper-

tension with a rather labile blood pressure. Simple exercise tolerance tests were carried out during which he complained bitterly of dyspnea and fatigue but the cardiorespiratory responses were within normal limits.

Not all patients with neurocirculatory asthenia could be tested satisfactorily in such an easy fashion. Sometimes it is very difficult to decide in these cases whether or not the heart is structurally normal. Investigators who have developed the more elaborate functional tests express great confidence in their methods. However, if a given procedure is heavily relied upon in deciding whether or not a heart is normal the only proof lies in a careful follow-up study which is seldom made.

Coronary Heart Disease.—The functional capacity of the heart may be determined as satisfactorily in coronary arterial disease as in other types of cardiac disorders. Even though the determination is accurate, however, it may offer little help, and, in fact, may be misleading. The reason is that functional capacity may not parallel the amount of coronary disease present. Because of this, functional tests are said by many to be inaccurate whereas, more properly, it should be said that a knowledge of the heart's capacity oft-times will not offer diagnostic or prognostic aid in coronary heart disease.

Too often, after a careful examination including a complete history, physical examination, electrocardiogram, and teleroentgenogram, there is insufficient evidence to make a diagnosis of coronary heart disease, yet within a few months the patient develops angina pectoris or coronary occlusion. On the contrary there is sometimes indubitable evidence of coronary arteriosclerosis and yet the patient lives without change of symptoms for years. For these reasons and because of the large incidence of coronary heart disease it is in this disorder more than any other that some helpful diagnostic and prognostic tests are needed.

To this end certain tests have been devised in addition to the usual exercise tolerance tests. These consist chiefly in determining the electrocardiographic changes or changes in the x-ray appearance of the heart when it is placed under a strain. At the present time these tests appear to be of a limited value. They need further study.

Summary and Conclusions.—Despite the fact that elaborate methods have been devised to measure the coincidental changes in the circulatory and respiratory systems both in health and in disease there is still insufficient knowledge to permit a clear generalization of the pathologic processes in the different grades of heart failure.

In determining the functional capacity of the heart many of the methods suggested, even the simpler ones, are very helpful. It must be emphasized that such determinations transcend the various types of heart disease and, at best, answer only the question how much work, at this time, is the heart capable of performing. This knowledge must be interpreted in regard to the particular problem under consideration. We have attempted to show under what circumstances a knowledge of the functional capacity is useful or misleading. It is our belief that the weak link in the problem of functional heart tests has been their interpretation; such tests have often been expected to answer questions that should never have been asked.

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GENERALIZED VACCINIA AND ECZEMA VACCINATUM

THE more frequent complications of vaccination such as urticarial or erythematous rashes, local lymphadenopathy and autovaccination by scratching of nearby or distant parts of the body, particularly the eye, are well known. That the danger of spontaneous spread of vaccinal infection is especially great in persons suffering from some affection of the skin is not so widely recognized.

Generalized vaccinia represents the occurrence of a generalized eruption of typical lesions following vaccination. This is of rare occurrence and of varying degrees of intensity, from a few scattered lesions with mild systemic symptoms to a course almost identical with variola. Most textbooks in mentioning the sequelae of vaccination include generalized vaccinia occurring either without evident cause or occurring in persons with debilitating illnesses or diseases involving the skin, particularly chronic eczema.

Eczema vaccinatum designates a type of generalized vaccinia following accidental vaccination by contact with a vaccinated person or a patient suffering from some skin affection, most commonly eczema, occasionally intertrigo, impetigo, or secondary syphilis. In not one of seven American texts is there mention of the danger to a person suffering from some skin disorder of contact with a recently vaccinated individual; in all of the German textbooks consulted, this danger is explicitly mentioned.

The first patient (Fig. 82), a five-and-one-half-year-old girl, an example of *generalized vaccinia*, was admitted to the hospital on August 25, 1936, because of a vesicular—later pus-

tular—eruption following vaccination. A paternal great-aunt had suffered from severe eczema; a sibling of ten months had eczema of the face and leg at the time of the patient's admission. Since the age of one year, the patient had had annual attacks of scaling, crusting, erythematous lesions involving most of the body. The eruptions occurred in midsummer and had persisted from one week to a month. The summer of admission,

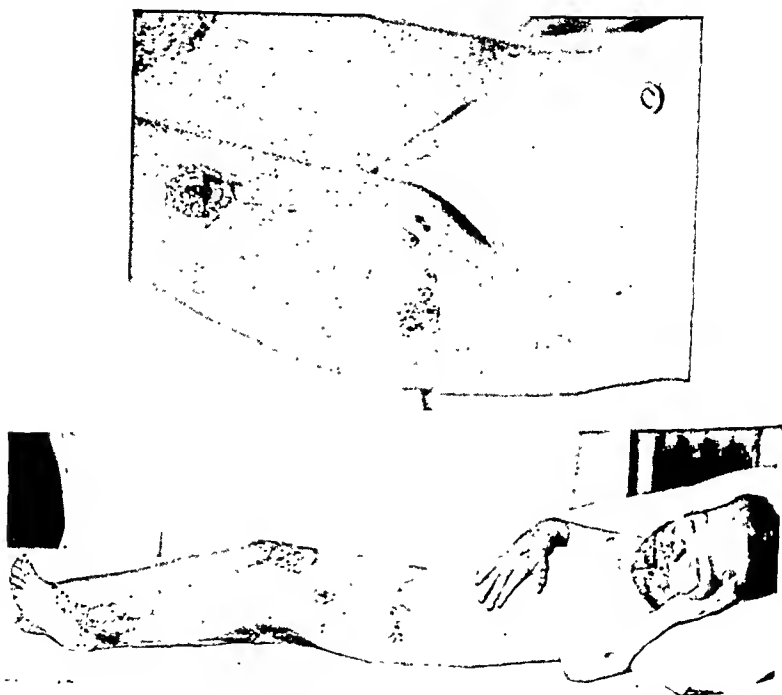


Fig. 82.—Generalized vaccinia in a patient vaccinated within a week following the subsidence of a widespread eczematous skin lesion. The vaccinal lesions are most numerous on the previously involved skin areas.

the rash, involving the left ankle, right knee, right hand and face, had lasted throughout July and had disappeared about the first of August. On August 7th the patient had been vaccinated on the lateral aspect of the left mid thigh. On August 10th, a papular itching eruption appeared over the areas involved in the earlier rash. Subsequently, the lesions became vesicular, then pustular. On August 14th, the original site of vaccination showed a normal large vaccination lesion.

On admission to the hospital, the temperature was 101° F. and the patient appeared moderately ill: there was generalized lymphadenopathy and a large crusted lesion with an erythematous base on the left thigh just above the knee. High on the left thigh were 6 to 8 umbilicated vesicles containing turbid fluid surrounded by zones of erythema, typical of vaccinia. Above the ankle on the left leg, on the right thigh above the knee, on the right forearm and wrist, and on both cheeks and about the mouth and chin were crusted, pustular, weeping areas.

The blood picture showed a leukocytosis of 30,000: the urine was normal. A smear of pus from the skin contained many polymorphonuclear cells and gram-positive cocci in pairs and short chains, on culture a hemolytic streptococcus.

On September 7th, 5 per cent ammoniated mercury was applied to persistent lesions with resulting severe irritative dermatitis. On the 10th, new lesions suggestive of vaccinia appeared on the left hand on the old eczematous lesions which had become weeping and had begun to spread. The temperature became elevated to 104° F.

Injection at this time of contents of the pustules into the skin of rabbits gave no typical vaccinal reaction. A blood culture was negative. After treatment with hot fomentations the skin gradually returned to normal.

The second patient (Fig. 83), a two-and-one-half-year-old boy, an example of *eczema vaccinatum*, was admitted to the hospital September 27, 1937. In this case there was no allergic family history. The patient had suffered from a chronic dry scaling eczema of the scalp and behind the ears since the age of four months. About the beginning of September, a three-year-old sibling was vaccinated. The 2 children were permitted to remain in close contact. On September 20th, the mother noted that the patient's eczema had become definitely worse, the child became fussy and irritable and was feverish. Four days before admission papular lesions appeared on the face.

The child was a small, poorly developed, rachitic male. The forehead, extending as far back as the region of the anterior fontanelle, and the skin about the left pinna were covered with an expanse of pus under a thin layer of epidermis from which a bloody, purulent discharge oozed in several

places. At the periphery of these areas, also on the lower lip at the left corner of the mouth, and about both lids of the left eye were discrete, umbilicated lesions 3 to 5 mm. in diameter filled with turbid opalescent material. On the tip of the tongue was a similar lesion. The lymph glands were generally enlarged, particularly in the cervical region. The liver and spleen extended 2 to 3 cm. below the costal margin. The temperature was elevated to 103° F.

Intracutaneous inoculation tests in rabbits were made by Dr. Morris Schaffer of the bacteriology department of the Har-



Fig. 83.—Eczema vaccinatum in a child suffering from a chronic eczema permitted to remain in contact with a child vaccinated against smallpox

vard Medical School on September 29, 1937, with material from the lesions. Precipitin tests with extracts of such material against sera from rabbits immunized to vaccinia were also carried out. Both of these tests were positive for vaccinia.

Seven days following admission, there were dried scabs on all the lesions except the larger areas of eczema. Six weeks later only the areas of eczema showed any scarring other than slight pigmentation. The liver and spleen had returned to normal size.

The procedure of vaccination has several sequelae which we often are unable to predict or to forestall, particularly generalized vaccinia and encephalitis. The generalized types of vaccinia described above, however, were predictable and might have been prevented by adequate care and investigation of the patients' personal and family histories.

In the first patient, vaccination was performed within a week following the subsidence of a widespread skin affection of eczematous character. In the second case, a child suffering from chronic eczema was permitted to remain in contact with a child vaccinated against smallpox. In both cases a generalized disease occurred with a vesicular, pustular eruption running a course similar to vaccinia but with shorter time intervals. In one case there was a reexacerbation of the process.

Generalized vaccinia following vaccination is mentioned in some of Jenner's later works. Cases of widespread vaccinia in persons with lesions of the skin but who had not been themselves vaccinated were reported in this country in 1882¹ by Martin and were termed *eczema vaccinatum*. The cases of generalized vaccinia in Germany from 1874 to 1904 were collected in a monograph by Blochmann,² a nonmedical man whose work was instigated by the loss of an eye from eczema vaccinatum in one of his own children.

Gins³ tabulated the reported cases in Prussia for the years 1913 to 1927 and found 12 cases of generalized vaccinia in persons vaccinated without preceding skin lesions, 11 cases in persons vaccinated in spite of preexisting skin lesions, and 10 cases in persons with skin affections, not themselves vaccinated.

The *age incidence* of generalized vaccinia is dependent on the usual time of vaccination in the first year of life and the predominance of generalized eczema in the same period. In 41 cases collected in the literature, 19 were in the first year, 16 in the period from the second to the fifth year and 6 cases in years above twenty, the range being from two weeks to forty-two years.⁴⁻³²

The fatality rate in 39 cases of eczema vaccinatum was 33 per cent: 2 deaths occurred in persons over twenty years of age, the others were scattered over the first five years of life. Blochmann² reported 6 fatalities among 20 cases of eczema vaccinatum.

Generalized vaccinia occurring in a patient himself vaccinated has appeared from four to as long as thirty days post-vaccination, *i. e.*, the generalized vaccinia might follow the same course as the original inoculation or come at a somewhat later date. In delayed cases, the course of the secondary lesion was much shorter than the primary. In some cases, successive crops of secondary lesions appeared as late as two to three weeks following vaccination.

The onset of eczema vaccinatum, estimated from the time of vaccination of the contact case in a series of 26 instances collected from the literature, varied from nine to twenty-three days with the largest number occurring from the sixteenth to the twentieth day. This suggests that the inoculation of the eczematous patient may take place at any time following the appearance of the vaccination lesion until the scab falls from the contact case.

The manner of contraction of eczema vaccinatum is supposedly by actual inoculation from the vaccinated person to the patient. The possibility of droplet infection of the skin of the eczematous patient is indicated in recent experimental work of Gins, Hackenthal and Kamentzowa³³ which has shown in 6 patients that vaccine virus may be isolated from the throats of vaccinated patients on the fourth and fifth days postvaccination but not before and not after. This was confirmed by rabbit and guinea-pig inoculation and recovery of virus from respiratory mucosa within two days postvaccination. These investigators also found that instillation of virus in the noses of rabbits conferred immunity only slightly less effectively than inoculation by the cutaneous route.

In eczema vaccinatum, the lesions are usually preceded by an exacerbation of the underlying skin affection.^{10, 5} Usually within three days after the exacerbation of the underlying eczema, a generalized papular eruption more or less limited to the areas of affected skin occurs. The papules rapidly become vesicular, umbilicated and pustular, in some cases within the space of twenty-four hours. Rarely do the lesions remain limited to the previously injured skin areas.

The degree of infectiousness of vaccinia is evident from the cases reported by Danziger¹² and Stümpke.¹⁹ The former reported a case of generalized vaccinia in a six-month-old in-

fant previously well without skin eruption with onset fifteen days after vaccination of a sibling; mother and grandmother had isolated lesions. This patient was brought to the open ward of an infants' hospital. Of 15 cases on the ward, 6 of whom were previously unvaccinated, 2 children with chronic eczema, 2 children with impetigo and 1 with secondary luetic rash contracted vaccinia. The luetic child died; only 1 eczematous child escaped. Stümpke reports 3 similar hospital cases secondary to an eczema vaccinatum.

That the immunity to revaccination even with the widespread lesions of generalized vaccinia is not permanent is shown by Busch's case²¹ of a child with chronic eczema who contracted eczema vaccinatum at the age of one and one-half years. Two years later with eczema still present, after contact with a vaccinated sister the patient suffered from recurrent eczema vaccinatum which proved fatal. This case was proved by demonstration of inclusion bodies in scrapings from the lesions. Lorbath-Jacob, Legrain and Solente²⁰ report the case of a patient forty-two years of age successfully vaccinated twelve years previously. Revaccination while suffering from an eczematous condition was followed in nine days by a generalized vesicular eruption. Sprengel¹⁸ reports a similar case.

The occurrence of sporadic cases of generalized vaccinia had been attributed to: (1) the exceptional virulence of the sample of virus lymph used, or (2) a constitutional sensitivity or lack of cutaneous resistance to the vaccine. In support of the former is the report of Froumy³⁰ who in revaccinating 175 cadets with 1 lot of virus had 120 takes, 12 cases of generalized vaccinia and 1 fatality. Geronne,⁶ Steinen,¹¹ and Schoedel⁵ found in using virus previously giving normal takes that not only did cases of generalized vaccinia occur, but that several members of the family had typical isolated lesions on the skin giving a positive Paul's test (rabbit cornea inoculation).

The course of generalized vaccinia and eczema vaccinatum is essentially the same. The disease may be very mild with few constitutional symptoms or may approximate malignant variola.²⁶ With the eruption, the fever may rise to 103° to 105° F., there may be generalized glandular enlargement, and in infants particularly hepatosplenomegaly is a common finding. The course of the fever is from seven to ten

days in uncomplicated cases; when secondary pneumonia or skin infection occurs, as in the first case presented, the temperature may remain elevated for a longer period. The fever is usually of the sustained type. Seldom do pitted scars result from generalized vaccinia; most of the scabs leave a smooth pink or brownish area corresponding to the erythematous areola. These areas gradually fade into normal skin color after several months.

The **diagnosis** of generalized vaccinia following vaccination of the patient should not be difficult. In eczema vaccinatum the contact with a recently vaccinated person can usually be elicited in the history. In differential diagnosis, one must consider variola and the nonspecific vesiculopustular complications of eczema first described by Kaposi and termed Kaposi's varicelliform eruption or as named by Juliusberg,³⁴ pustulosis vacciniiformis (or varioliformis) acuta. An absolute differentiation from mild variola is extremely difficult inasmuch as severe vaccinia can run the same course as variola and in some instances has been proved moderately communicable. Tedder³⁵ has recently discussed the possibility that some cases of nonspecific vesiculopustular eruptions may in actuality be true eczema vaccinatum despite the absence of history of contact.

The differentiation of the nonspecific secondary infections of eczema can be accomplished by:

1. Finding of inclusion bodies in biopsies of fresh material.
2. Inoculation of the contents of a vesicle by scarification of a rabbit's cornea (Paul's test). The virus if present will produce a keratitis in which the typical inclusion bodies may be found.
3. Intracutaneous inoculation of vesicular contents in a rabbit. This test gives a higher percentage of positive results than Paul's test.
4. A test described by Gordon, Burgess, Tulloch, and Craigie,^{37, 38, 39} consisting of a flocculation reaction of extract of the lesion against serum produced in rabbits. According to Ledingham^{40, 41} there is greater flocculation of vaccinia bodies against vaccinia immune rabbit sera than against variola immune rabbit sera and vice versa. This specificity is lost on passage of the virus through a rabbit.

A positive result in any of the above tests definitely rules out Kaposi's varicelliform (vacciniform) eruption.

In treatment of generalized vaccinia, Evans²⁹ has suggested the use of immune serum or of transfusion from a person recently successfully vaccinated. This procedure may be of value in preventing the occurrence of further lesions and in combating the severe toxic action associated with the spread of the virus. Local treatment of the lesions may prevent escape of the infectious material to uninfected areas or to other persons.

Intracutaneous vaccination which does not produce a surface lesion has been recommended for prevention of eczema vaccinatum and generalized vaccinia. Nobel⁴² has reported 74 cases of intracutaneous vaccination in eczematous children with no secondary lesions. This method fails to take into account the evidence that virus is present in blood stream and recoverable from respiratory tract mucous membranes in the course of ordinary vaccination.

Vaccination apparently should not be performed except under extreme circumstances in a person suffering from a skin affection, acute or chronic, or an acute or debilitating disease. The danger of a recently vaccinated person to individuals in the environment who are suffering from a skin disease, particularly eczema should not be overlooked. In the words of Groth,⁴³ "The field of contraindications (to vaccination) compasses not only illnesses in the patient himself but also illnesses in persons in his environment. Impetigo, purulent and erysiploid processes, measles, scarlet fever, diphtheria and above all eczema in a member of the household of the person to be vaccinated demands the postponement of the vaccination."

Whether intracutaneous vaccination will eliminate dangers of generalized vaccinia in patients with skin disorders remains to be seen.

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TREATMENT OF INFANTILE ECZEMA

INFANTILE eczema is a problem that faces the dermatologist, the pediatrician, and the family physician. In fact, even the druggist and neighbor get their chance at treating this condition.

What follows is simply an attempt at classification and a statement of the treatment that has proved most successful in the hands of the author.

Infantile eczema may be divided into two types:

1. The type that is limited to the face, particularly the flush areas.

2. The type which involves the scalp, face, preauricular and postauricular areas, the upper and lower extremities, and the small of the back. At times other areas become involved. It is this type that later in life shows a rather persistent involvement of the flexures of the elbows and popliteal spaces (neurodermatitis, atopic dermatitis). The lesions may be dry and scaly on erythematous bases, but in most instances are moist and crusted (particularly in the flush areas of the cheeks). Itching is usually marked. In spite of all, the baby usually appears healthy.

The first type shows a chapped-like condition of the face and is traumatic in origin, arising from exposure to sun, wind, and soap and water.

The second type is the more complicated one and may be further classified as follows:

- (a) Sensitization eczema (atopic dermatitis).

- (b) Mycotic eczema.

- (c) Combined sensitization and mycotic eczema.

Sensitization Eczema (Atopic Dermatitis).—This type may be due to endogenous factors or exogenous. The former

are the products of body metabolism and reach the skin through the hematogenous route. By exogenous factors are meant not only substances which come in contact with the skin, but substances such as food proteins and medicaments which are ingested and reach the skin by way of the blood. Jadasohn and Block¹ stressed the importance of exogenous factors in the etiology of eczema in adults. Peck and Salomon² stress its importance also in infantile eczema. Rost³ and his school stress the importance of the metabolic factors and claim that the exogenous factors play a minor rôle.

The consensus of opinion at present is that the exogenous factors play a more important rôle, but even here there is a diversity of opinion for some believe that infantile eczema is in the majority of cases caused by allergens brought to the skin through the hematogenous route, as in the case of foods, whereas others believe that as in most adult eczemas contact with a substance from without is the chief factor.² I believe that in the case of infantile eczema both play a part, but that the hematogenous route is the most common.

General Discussion of Skin Tests.—Skin testing is a method of determining the causative agent in infantile eczema, particularly the allergic type. Although it is more satisfactory in infants than in children and adults, its efficacy in detecting the specific causative agents is still debatable. Thus far we can simply state that positive skin reactions indicate a phase of allergy in that child (specific sensitization which may not be related to the present symptoms of the patient). Not too infrequently the removal of such offending agent does not bring about improvement in the eczema.

There are four methods of testing:

1. Cutaneous.
2. Intracutaneous.
3. Passive transfer (Prausnitz-Küstner phenomena).
4. Patch testing.

Patch tests according to S. Peck and Salomon is as important in infantile eczema as it is in adult eczema. They state "The pathogenesis of eczema in infancy and childhood does not differ from that of eczema in the adult. The eczema is caused as a rule by contact with a substance from without. Less frequently the allergen may be brought to the skin hemat-

ogenously, as in the case of foods." This, however, is a matter of opinion.

The most offending foods are found to be (in order of importance) eggs, milk, wheat, barley, spinach, oat, beef, corn, potato, and tomato. It has also been found that if the patient is sensitive to cow's milk he is as a rule sensitive to other forms of milk such as goat's milk.

The treatment of infantile eczema is not a specific one and therefore what applies to some cases does not apply to others. In the first type, the traumatic type, it is essential to remove all possible external irritants, and use a mild, soothing application. The following medications have been found useful in these cases:

R	Zinci oxidi.....	℥ss
	Amyli.....	℥ij
	Petrolati.....	℥j

M.

To the dry scaly areas.

R	Acidi salicylici.....	gr. v
	Bismuthi subnitrat.	℥ss
	Amyli.....	℥ij
	Ung. aquae rosae.....	ad ℥j

M.

To the dry scaly areas.

R	Zinci oxidi.....	℥ij
	Calamini.....	℥j
	Phenolis.....	℥ss
	Glycerini.....	℥ij
	Aquae dist.	ad ℥viij

M.

Used as an antipruritic.

A grain of menthol to the ounce of the above lotion may be added in cases of marked pruritus.

Protect against wind and too much sun. A superfatted soap is advisable for bathing purposes.

Mycotic Eczema.—In the case of proved mycotic eczema, hunt for the source particularly in the mother's hands. The author can cite several instances where the identical organism was isolated from the mother's hands and the baby's eczema. It is then essential to treat the mother's hands in conjunction

with carrying out the treatment of the baby. In spite of its being an infection, we advise against the use of soap and water because of the possible trauma that may be produced, which in turn lowers the resistance of the surrounding skin thus spreading the infection. Warm boric acid solution in the form of either compresses or simply washing is the best method of cleansing the skin.

The itching is usually eliminated by the use of the following antipruritic lotion:

R̄	Mentholis.....	gr. viij
	Zinci oxidi.....	ʒij
	Calamini.....	ʒj
	Phenolis.....	ʒss
	Glycerini.....	ʒij
	Hamamelis.....	ʒss
	Aquae dest.....	q. s. ad ʒviij
M.		

This may be used several times a day and is followed at night by the application of one of the following ointments:

R̄	Mercurochrome crystals.....	gr. x
	Aquae.....	℥xx
	Acidi salicylici.....	gr. xx
	Petrolati	
	Lanolinis.....	āā q. s. ad ʒj
R̄	Acidi salicylici.....	gr. xv
	Sulfuris praecipitatis.....	gr. xv
	Petrolati.....	q. s. ad ʒj

With the improvement of the eczema the patient should be gradually weaned away from the ointment used rather than suddenly stopping because of the possibility of recurrence. For the various dressings to be used on the skin see the paragraphs on nursing care (to be discussed later).

Treatment of Sensitization Eczema.—In this type of eczema a thorough history is very important. The history should include questions such as “Is there any history of asthma, hay fever, urticaria, or eczema on the maternal or paternal side?” “Is the baby breast fed?” If bottle fed. “What is the formulary and how does the infant take it?” “What is the appearance of the stools?” If the baby is one

to two years of age, "What is he eating?" "Does he vomit?" "Is the eruption aggravated in relation to the ingestion of certain foods?" Questions about contacts such as clothing, bedding, and animals should be included. Very frequently the answers to these questions may give us a clue to the offending agent. Although I stated before that skin testing to foods is not absolute, yet the tests should be done and in some instances will help toward finding the offending factor or factors. Patch testing should also be done because in a number of these infantile eczemas there is a combination of protein sensitization and contact sensitization.

Peck and Salomon have found chicken and goose feathers common offenders in these cases of infantile eczema. I would suggest therefore that this be born in mind in the treatment of these cases.

Feeding Problem.—There is no one dietary measure that is uniformly successful. In cases with positive skin tests to foods, the corresponding foods should be omitted, but great caution must be exercised to avoid deleterious results from removing from the diet too many foods for a long period of time. Eczema is a much less serious condition than a malnourished infant with a resistance low enough to pick up one or more secondary infections. The three most common offending foods are eggs, milk, and wheat. These foods should be suspected even in cases of negative skin tests. History of the aggravation of the condition relative to the ingestion of a food is frequently a great help. The results of dietary regulation in accordance with food tests are more successful when there is a definite sensitization to one or two foods as indicated by positive tests. Numerous positive tests are rather misleading.

In bottle-fed babies, Blackfan, Schloss, Hill and others advocate a milk-free diet even though the skin tests are negative. Hill and Stuart¹ suggest a substitute known as sobee, a food made of soy bean flour, olive oil, purified corn starch, and various salts. Heated milk, because of the possible change in the protein caused by heat is at times tolerated where raw milk is not.

In breast-fed babies, the mother's diet is of importance. Many mothers still feel that cocoa, egg nogs, cereal, and other rich foods are essential for the increase in the quantity and the

improvement of the quality of the milk. This, of course, is not so. Chocolate in particular is an offending agent.

In the majority of cases the local treatment is still the most effective weapon that we have.

Local Treatment.—Itching is severe in most cases and the baby does a good deal of scratching with resulting trauma of the skin and secondary infection. If scratching could be eliminated the condition would improve much more rapidly. This should be done with the least punishment to the baby. A discussion of the various means of keeping the hands away from the involved areas will be found in the paragraphs on nursing care. I have found soap and water harmful in these cases and feel that they should be eliminated. Mineral oil is a good cleansing agent, but one must first make sure by patch testing that the infant is not sensitive to mineral oil. If the child is sensitive to mineral oil, a vegetable oil such as olive oil or peach kernel oil may be used. It is important not to leave the oil on the skin but to gently dry it because if allowed to remain on the skin it may act as an irritant. Antipruritic lotions should be used and used frequently. The following lotions and their many variations have been found helpful:

R	Zinci oxidi.....	5ij
	Calamini.....	5j
	Phenolis.....	5ss
	Glycerini.....	5ij
	Aquae dest.....	q. s. ad 3viiij
M.		

or

R	Zinci oxidi.....	5ij
	Calamini.....	5j
	Phenolis.....	5ss
	Liquor calcis.....	ad 3viiij
M.		

To either of these may be added a grain of menthol to each ounce to increase the antipruritic effect. In some cases the omission of the zinc oxide and calamine with the addition of the menthol and witch hazel $\frac{1}{2}$ to 1 ounce to the 8-ounce mixture is found to be very useful as an antipruritic. In place of the menthol one may add liquor carbonis detergens 1 drachm to the 8-ounce mixture of the first of the two lotions.

At night one of the following ointments:

R	Crude coal tar.	5 ^{ss}
	Zinci oxidi.	5 ^{ss}
	Amyli.	5ij
	Petrolati.	3j
M.		
R	Crude coal tar.	5 ^{ss}
	Zinci oxidi.	5 ^{ss}
	Petrolati.	3j
M.		

is applied after the lotion has dried on and allowed to remain on until morning when it is removed gently with oil. If there is very much oozing and moisture the ointment may be used morning and night.

Caution.—The child should not be kept in the sun while the ointment is on because of the possible dermatitis from the sun. Watch for glandular enlargement or pustulation and if they appear omit the ointment.

In case of secondary infection superimposed upon an eczema the following ointment is useful:

R	Mercurochrome crystals.	gr. xx
	Aquae.	℥ xx
	Acidi salicylici.	gr. xx
	Lanolinis	
	Petrolati.	āā ad 5j
M.		

Occasionally, in the moist cases, the use of straight crude coal tar for a short period will eliminate a good deal of the oozing and then the other ointments may be used. When the stage of dryness and scaling is reached, then the following ointment should be substituted for the crude coal tar:

R	Zinci oxidi.	5 ^{ss}
	Amyli.	5ij
	Petrolati.	5j
M.		

The scalp is usually involved in these cases and there either the mercurochrome ointment or the following ointment may be used:

R	Acidi salicylici.	gr. xv
	Sulfuris præcipitatis.	gr. xv
	Petrolati.	q. s. ad 5j

Recently there have been a number of white tar ointments put on the market; thus far I have found that none of them can take the place of the straight crude coal tar ointment.*

Combined Sensitization and Mycotic Eczema.—In this type the eczema may occur first and then the superimposed fungus infection. Or, because of the fungus infection in a potentially allergic individual, the threshold of sensitivity is lowered and thus the resulting eczema.

The treatment of this type of eczema is practically the same as the treatment of sensitization eczema with the mercuriochrome ointment proving the most effective. Look for a possible source of infection.

Nursing Care.—One cannot treat the infant with eczema as one would treat a baby who is ill, as the eczema rarely makes the infant ill. It is therefore necessary to have patience, ingenuity, and resourcefulness. The child must be prevented from scratching and yet allowed his freedom of movement. It is essential that dressings be placed over medications because you cannot reason with the infant about allowing it to remain on otherwise. For the face a mask may be made from an old cotton pillow case (the material is usually softer than newly purchased cloth), be sure it fits the head well, cut holes for the eyes, nose, and mouth. Close at the top and back by either sewing or pinning with small safety-pins. A fresh mask must be used with each application of medications, the old one may be boiled and used again. Bandages may be used in place of the mask but the mask, properly fitted, proves best. For restraining the hands so that the child will not scratch, one may use cuffs (to keep the child from bending his elbows so that he cannot reach the face to scratch), long sleeves which may be closed over the hands (these are best for sleeping since they may be tied to the sides of the crib allowing the child enough motion for comfort), or stockings to be pulled up over the hands. The cuffs are preferred because the patient still has the use of the hands and is thereby more contented. The cuffs are made by placing cardboard over the sleeve of the undershirt from the axilla to the wrist and pulling the cuff of the undershirt up over the edge of the cardboard cuff. Then

* Mix zinc oxide and crude coal tar and allow to stand several hours. Then add petrolatum, working it briskly.

bandage the cuff securely and pin the bandage at the back of the arm.

The choice of clothes is also very important. It is essential that the child wear either cotton, soft linen, or silk next to the skin. Wool should never touch the skin as it can cause recurrence of the skin condition through irritation. If the child must wear wool to keep warm, be sure to have the wool placed over cotton, linen, or silk. Bleached cotton cloth is the most practical because of the stains from medications which make daily boiling essential.

Baths.—The bathing of the eczematous baby is a very important part of the treatment, and since soap and water is often contraindicated, the medicated baths must be relied upon. They not only cleanse but also soothe and quiet the sensitive skin. The following are some of the types of medicated baths used:

Cornstarch Baths.—This is a simple, practical, inexpensive bath. It can be used to relieve either itching, burning, or irritation and when there is considerable exudate. The directions for the bath are: "Use sufficient cold water to dissolve $\frac{1}{4}$ box of cornstarch. To the solution add 1 quart of boiling water. Then pour the mixture into a bath tube $\frac{1}{4}$ full of warm water (or a bathinette full of warm water), 90 degrees in temperature."

Oatmeal Baths.—Especially of value when there is complete exfoliation of the skin. It is also recommended when the cornstarch bath proves too drying. The directions for the oatmeal bath are: "Pour one pint of boiling water over one cup of oatmeal. Cook on the stove until a thick porridge is formed. Fill the bathtub $\frac{1}{4}$ full of warm water at 90 degrees (or bathinette full) and dissolve in it $\frac{1}{8}$ cup of baking soda. Pour the porridge into a cheesecloth bag and tie securely. Swish this porridge bag around in the tub, stirring up the soda, until the water is milky white. The porridge can be used as a sponge to wipe over the patient and to remove old medications and dried scales."

Boric Acid Baths.—Valuable when there is extensive superimposed secondary infection. The directions for the boric acid bath are: "Dissolve one half pound of boric acid crystals in a

tub one quarter full of hot water. Cool to the desired temperature."

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THE RECOGNITION AND TREATMENT OF ADOLESCENT ENDOCRINE DISTURBANCES

THE present knowledge of endocrine diseases is still indefinite enough to make it difficult for a clinician to answer many of the questions asked him by his patients. The proportion of brilliant cures of obscure complaints has been large enough to stir the imagination of the nonmedical world and the publicity given to treatments of this sort has caused the public to hope for relief from almost any symptom which does not respond to standard treatment, whether it be endocrine or not. As a result, combinations of glands are now on the market which propose to correct many of the obscure ills from birth to old age. The fallacy of this type of therapeutics need not be emphasized.

Although there are definite conditions, such as cretinism, myxedema, goiter, diabetes, and parathyroid tetany, that are fairly well understood and for which there are established methods of treatment, there are many other syndromes about which very little is known. Some light has been thrown on the action of all the glands, but it seems improbable that their physiology will be as well understood as that of other organs and systems until methods are devised to measure each of the circulating hormones in the human body. When such tests are perfected and simplified it will be possible to measure the amount of the hormone which is probably acting at a given time and thus make clearer the action of individual glands as well as their effect of one upon another.

The crude means and methods of diagnosis now available must be used with care because hardly any physiologic reaction is known to belong specifically and only to an individual

gland. Failure to take this into account and lack of knowledge of the normal range of action has led to many unwarranted diagnoses and much unneeded and unjustified treatment.

It is the purpose of this clinic to discuss some of the tests which are performed in collecting data on which a diagnosis is made. They fall into two groups, the first of which is clinical and depends upon careful and accurate observation, and the second, laboratory data. They are discussed in the order in which they may be considered in clinical practice.

Growth.—The skeletal growth of the body follows a general upward trend with advancing age and is usually recorded in the terms of standing height. The standard which is commonly used for children is that which bears the name of Baldwin-Wood, and is based upon measurements of public school children obtained more than twenty years ago and averages somewhat lower than would a similar set of measurements taken today. Children attending private schools average taller than those in public schools. It is a well-known fact that the American race is growing bigger. Therefore the assessment of growth in relation to the endocrine glands, especially in gigantism, must take into consideration the superior growth of this decade. Gigantism in the child and acromegaly in the adult have been shown to be due to oversecretion of the anterior part of the pituitary gland. Let us suppose that a girl of nine years has been brought to us with the question of pituitary pathology because she has outgrown all her friends of the same age. How much emphasis should be given to her superior growth in considering the diagnosis? The answer cannot be arrived at on one visit and can only be reached after prolonged study. Such growth may not be and probably is not pathologic. It may be due to favorable economic circumstances with better food, both in quantity and quality, to better hygiene, or to few illnesses. Very often early superior growth only anticipates the normal growth which would have come later. Such children reach their maximum height at an age much earlier than the average. This nine-year-old girl might reach her maximum height at thirteen years instead of the usual average age of sixteen years. It is known as anticipated growth and is not pathologic. Overgrowth then cannot be considered abnormal until it has progressed beyond normal

limits. Superior height is of less significance in families that are hereditarily tall than in families in which the trend is to attain only average height or to be short. How high the normal limits will eventually reach will only be determined by experience and time.

Deficient growth or dwarfing is known to be present in cases with deficient pituitary gland and hypothyroidism. Yet the primary and principal cause of deficient growth may not be endocrine. It may be due to lack of food and growth-promoting vitamins, continued illnesses, poor hygiene, and hereditary causes. Many cases of dwarfing were seen in Europe as the result of starvation during the World War. It is difficult to assess the relative importance of the various endocrine glands. It is known that the pituitary has a growth hormone and yet to date the administration of various pituitary-growth hormones has been attended with indifferent and variable success. The growth hormone developed by Collip seems to be the most effective. The conclusion that treatment was successful in some of the cases reported is unjustified in many cases, since the growth curve was no greater than would have been expected without treatment and did not speed up or approach the expected height for the age. A few reports, however, have recorded superior growth which did not seem to be connected with the onset of puberty and may have resulted from the treatment. The evaluation of any therapeutic agent, the purpose of which is to accelerate growth, must always make allowances for the growth that is to be expected normally at the age.

Abnormalities in growth of separate parts of the body should be considered in diagnosis. The dwarfing in cretinism is accompanied by shortening of both the arms and legs which becomes more pronounced with increasing age. During normal infancy the length of the legs measured from the sole of the foot to the pubis is approximately three eighths of the total height and that the vertex to the pubis is five eighths. These proportions gradually change until adult relations are reached and the pubis is midway in the length of the body. Growth may be so stunted in the cretin that the infantile proportions persist in untreated adult cretins as is shown by the characteristic shortness of the arms and legs. The dwarfing

of achondroplasia should not be confused with that in hypothyroidism because it is due primarily to shortening of the humerus and the femur without corresponding changes of the other long bones. There should be no trouble in differentiating these two conditions, especially since the achondroplasiac has a normal and the cretin a backward mentality. Mongolianism, which is sometimes confused with cretinism, should be easily recognized by its characteristic physical signs. The most striking of these are the palpebral fissures which are tipped upward at the outer sides, the button-like end of the nose, red cheeks, fine soft skin and hair, characteristic grimaces, the mongolian appearance, and a bizarre combination of other physical abnormalities.

Excessive length of the arms and legs in which the former may reach nearly to the knees is said to be characteristic of certain types of hypogonadism and eunuchism. Unusual disproportions of arm length may be determined by comparing the span length of the arms with the height. Normally the span equals the height. When it exceeds the height by 5 to 6 cm. it probably is unusual.

Growth of the bones can be determined by means of the x-ray. Usually this is accomplished by comparing closure of the epiphyses and the development of the various centers of ossification of the wrists with those of normal children of the same age. Various standards of epiphysography have been recommended. Those of Englebach and McMahon¹ and of Skelton² are in most common use.

Hypothyroidism is the most common condition during pre-adolescence showing retarded ossification of the centers of the wrist. It is believed by some that even relatively mild disturbances of the thyroid can be recognized by this means. If hyperthyroidism continues over a long time it may be associated with premature appearance of the osseous centers. These findings are corrected by thyroid therapy.

Deficient calcification of the bones due to withdrawal of calcium from the skeleton is seen in hypoparathyroidism.

The centers of ossification appear at the normal time in pituitary dwarfism. In hypergonadism the centers of ossification appear at the normal time but the epiphyses unite earlier than usual, while in hypogonadism the epiphyses unite late but

the centers of ossification appear normally. In cases of neoplasm the findings may be distorted by sympathetic action of other glands.

Although there is reported evidence that extracts of the thymus and pineal can affect the growth of rats, there is no evidence which shows that either have any effect on the growth of human beings. They, therefore, cannot be considered in treatment with the present state of our knowledge. Marked growth usually results from thyroid therapy in cases of hypothyroid dwarfism.

The foregoing statements while based upon much evidence cannot be accepted as final until more accurate measurements of gland activity are available.

Sex Development.—Much has been written and little is proved. There is suggestive data which seems to indicate that hyperactivity of the glands is associated with vigorous and sometimes precocious sexual development. The gonadotropic hormone of the anterior pituitary is considered by many to be the most important element in sex development. With it the pineal, suprarenal cortex and the gonads must be considered in differential diagnosis. Oversecretion of the adrenal cortex in the female has been shown to cause women to take on male characteristics, such as a deep voice, excessive growth of hair with male distribution, at times a moustache and beard, underdeveloped breasts and a male shape of the body. In the most pronounced cases genital abnormalities of various degrees develop and when extreme the male sexual characteristics are so pronounced that the sex of the individual is in doubt. This is known as hermaphroditism. Tumors of adrenal cortex may lead to masculinization of either sex. There are no cases in the literature in which the thymus was proved to be connected with precocious sexual development. Those that are due to the pineal are usually not diagnosed until symptoms of pressure appear. Granulosis of the ovary must also be considered. The differential diagnoses of these conditions is very difficult. It is rarely made medically, sometimes is possible by surgical exploration, and is usually only definite after postmortem examination. Treatment depends on diagnosis.

Backward Sexual Development.—There is considerable racial and family variation in the age that both the male and

the female develop sexually. The inhabitants of tropical countries tend to mature earlier than those living in colder climates; some families mature early and others late. It is, therefore, important to study the family history in estimating the normality of maturity. Fertility also has been modified to such an extent by various influences that if it were not for increased longevity the population of many nations would now be diminishing. So far as is known today the glands that take a part in normal sexual development are the pituitary, thyroid, suprarenal cortex, and the sex organs themselves. Lack of the necessary hormone of one or several of these glands may be associated with retarded or absent development of the gonads. Although deficient secretion of the pineal and of the thymus theoretically might do the same, it has never been proved to happen in the human being. These two glands therefore need not be considered.

The anterior part of the pituitary gland is of most interest in this connection since it is known to secrete a thyreogenic, a cortogenic, and a gonadotropic hormone, as well as other hormones connected with milk secretion and the menstrual cycle. The recently devised tests for evaluating some of these hormones in the urine are adding valuable knowledge to the subject. Adult male castrates have no testes hormone in the urine or blood but continue to excrete prolan in the urine.

Cryptorchidism (Undescended Testes and Backward Genital Development).—Evidence to date indicates that a proportion of the cases with this condition are due to a disorder of the pituitary gland. Those in which there is diminished or lacking urinary prolan respond most favorably to antuitrin S. Critical study of a large number of carefully studied cases should define more accurately than is now possible its limitations and indications for its use, but many brilliant cures have been reported.

Obesity.—Obesity is a symptom not uncommonly seen in otherwise normal individuals and has been attributed to dysfunction of the pituitary, thyroid, gonads, adrenals, and pancreas. Probably most cases of obesity are either normal or are not actually obese. A child is said to be obese if he weighs more than 20 per cent above his expected weight for his height. Although this criterion usually does not lead one

astray, it has been found that if the amount of muscle tissue is estimated from the creatinine output there may be wide discrepancies between the obesity estimated by means of the height-weight charts, by clinical observation, and by urinary creatinine method.³ Since creatinine measures the amount of muscular tissue in the body, its measurement should give the most accurate picture of the relative body makeup. It should be used in all cases in which it is essential to know the amount of "active" or muscle tissue in the body.

One of the most common forms of nonendocrine obesity is overeating and laziness. Some people with good digestions find it difficult to keep their weight down even when taking reasonable amounts of exercise.

Endocrine disturbances to which obesity has been attributed are deficiency of the anterior pituitary, the gonads, the suprarenal cortex, and the thyroid. The latter is not true obesity, in which the relative amount of fat in the body is increased, but is myxedema. The influence of the pituitary gland on the carbohydrate and fat metabolism may have some bearing on the development of obesity. It is most marked in the combined deficiency of the pituitary and the gonads. Most clinicians diagnose any case of marked obesity in childhood as Fröhlich's syndrome or a "typical pituitary case" without further thought. This point of view is unjustified since the physiology and pathology of obesity is by no means clear.

If a case of so-called "Fröhlich's syndrome" is being studied, the following factors in the history must be taken into consideration. Frequently the onset of the obesity in these cases is preceded by a history of severe infection. Such a history is very suggestive and it was present in the case of W. N. who was a typical case.⁴ If, on the other hand, there is a family history of obesity handed down through generation this might be interpreted either as faulty food habits or a family tendency toward some pituitary abnormality. The typical male cases of Fröhlich's syndrome or adiposogenital dystrophy develop female characteristics such as enlarged breasts, prominent mons veneris, tapering fingers and hairless skin, and a female distribution of fat over the body, with excessive fat around the pelvic girdle, and relatively tapering legs. Such physical development is more impressive and important in the male than

in the female. In the female the most important symptom is delayed adolescence and onset of catamenia. Such a delay makes one suspect that there might be trouble in the pituitary or its neighborhood, but such a history has less weight in families in which the trend is to mature later than the average. A definite diagnosis cannot be made on this data alone, nor are we helped much by the high sugar tolerance test which is present in this and other types of obesity. Roentgenography of the sella turcica nearly always gives negative data and very rarely do the visual fields aid us. The Laurence-Moon-Biedl syndrome, the characteristics of which are retinal pigmentary degeneration, obesity, mental deficiency, genital dystrophy, and polydactylism, is confused with Fröhlich's syndrome and their relationship is not understood.

Basal Metabolism.—The interpretation of basal metabolism of children is more difficult than that of adults because childhood is a period of continual change. Furthermore, standards which do not allow for the physiologic differences which may influence the metabolism give results that may lead to unwarranted conclusions. Children with a normal physical development can be compared with almost any established standard, but those that are obese or much underweight should be studied by special methods. The same may also be true of the very tall and of dwarfs. If this is done, results which give very accurate information can be obtained.

It is not necessary to enter a discussion of the various metabolism standards for children because I have done this many times in the literature. Nevertheless, emphasis should be given the fact that muscle represents most of the heat-producing tissue and its amount can be measured by the urinary creatinine, and that fat, water, and bone do not produce heat. Since the latter have weight it is obvious that any standard which includes weight in its formula, as do both the body surface and the multiple prediction formulas, will give seemingly low figures in obesity and high in malnutrition. That these figures do not represent the true relationship to the normal heat production is shown by the fact that when the actual total amount of heat produced is compared to that produced by children of the same height and sex the metabolism is normal. I have recalculated the metabolism of many cases

of obesity in these terms and have found that contrary to the reports in the literature the metabolism of obesity, instead of being low, is in practically all instances a high normal. Clinical therapeutic tests with thyroid have confirmed the validity of this conclusion. In malnutrition the metabolism instead of being high is below normal. Standards giving the expected metabolism for the height and for the weight of children of both sexes can be found in the American Journal of Diseases of Children, 55, 455, 1938.

Hypothyroidism is associated with a depressed metabolism and hyperthyroidism with an elevated metabolism; the former may reach minus 40 per cent and the latter plus 60 to plus 80 per cent. The adrenal gland also affects the basal heat production which is increased by adrenalin and diminished in Addison's disease. It has also been found low in deficiency of the gonads. Exception to this is the fact that the basal metabolic rate is probably not influenced by the male sex hormone.

Blood Pressure.—The blood pressure runs parallel to the basal metabolism. A blood pressure elevated to the height of a case with essential hypertension, without a corresponding increase in the heat production, is associated with basophilic adenoma of the pituitary. Such high blood pressure, although rare in childhood, may be found in other conditions such as nephritis.

Electrocardiogram.—In cretinism of marked hypothyroidism the T wave is flat. This interesting finding, however, has not been of clinical importance since it has been recorded to date only in marked cases in which the diagnosis is unquestioned.

Chemical and laboratory tests which also aid in differentiating some of the endocrine disturbances are as follows:

Low blood calcium is found in parathyroid tetany and high blood calcium is seen in hyperparathyroidism and is associated with decalcification of the bones. Overproduction of the parathyroid hormone may be present without hypercalcemia. The usual form taken by clinical hyperparathyroidism is generalized osteitis fibrosa cystica. Tetany which is not due to pathology of the parathyroid gland is associated with a low blood calcium. It is most frequently seen during infancy associated with rickets and a change in the blood phosphorus.

Blood Potassium.—The lack of adrenal cortical hormone in animals leads to a high blood potassium, and large doses of cortin administered to normal human beings causes a reduction in the sodium excretion and an increase in the potassium excretion. The exact significance of this is not known, however, and it is not yet of diagnostic clinical value.

Blood sugar tolerance curves are of interest in two conditions. A curve rising very high means a low tolerance to sugar and is found in diabetes mellitus. A curve which rises very little means a high tolerance for sugar and is frequently seen in obesity. Although a high sugar tolerance is found in pituitary deficiency it is also seen in other types of obesity which may have no direct relation to endocrinopathies. The importance of the sugar tolerance curve is, as yet, not clearly defined and too much emphasis should not be placed on it.

Blood Cholesterol.—Much emphasis has been laid upon the relation of the blood cholesterol and the thyroid gland. In cases of myxedema it is usually found much elevated and in toxic goiter depressed. It has been suggested as a test to replace basal metabolism determinations, but since the cholesterol level of the blood can be affected by other conditions it cannot be depended upon to give accurate knowledge. Its physiology should be studied further to determine exactly what it represents in the endocrine metabolism. For example, in deficiency of the posterior pituitary gland there is a marked rise in the blood cholesterol after meals which can be prevented by an excess of pituitrin.

Although there is an inverse correlation between the basal metabolic rate and the blood cholesterol, these two measurements do not change simultaneously. Since it is generally accepted that the main regulator of the heat production is the thyroid gland, the fact that the metabolism and the cholesterol level change independently of each other suggests that some other factor than thyroid may be influential in determining the cholesterol level. Adrenalectomy and nephrosis are accompanied by a high blood cholesterol. The latter is not accompanied by a low metabolism as has been assumed. The seeming lowering of the heat production is due to the edema characteristic of these cases and not a true lowering of the heat production.

Water Balance.—A disturbance of the water balance is shown clinically by the excretion of excessive amounts of water through the kidneys. This is compensated by the ingestion of large amounts of water and is known by the name of diabetes insipidus. The urine is of a very low specific gravity but is otherwise normal. The daily total excretion of chlorides and nonprotein nitrogen is close to normal and the chemical constituents of the blood remain normal. Although it can be controlled by the injections of solutions of the posterior pituitary, such treatment is often accompanied by unpleasant symptoms. Considerable success is reported by intranasal applications which are free from unpleasant symptoms.

Urinary Hormones.—Recently the measurement of hormones excreted in the urine has been added to the tests which give indication of the action of the endocrine glands. The follicle-stimulating prolan has been measured in numerous cases and estrin has been found to be present in small amounts in children of eight years and older. The knowledge obtained from the latter test has not been very useful as yet.

The test for prolan in the urine has been used to determine if abnormality of development of the genitalia is primary or is secondary, whether it is due to deficiency of the gonads themselves or deficiency of the gonadal-stimulating hormone of the pituitary. There is suggestive evidence that cases in which it is deficient react better to specific therapy than those in which it is present in normal amounts. In primary gonadal insufficiency and after castration and menopause the urinary prolan has been reported high. In pituitary failure it has been reported low. Estrin is found present in the blood and urine of the female and androsterone in the male; they are said to be low in hypogonadism. Although these tests promise much interesting and important information as they become refined, their use with adults or after puberty should be more helpful in diagnosis than with young children. Much has yet to be learned about their physiology before they become of routine usefulness in clinical practice.

These tests are presented and an attempt is made to evaluate them. Their limitations are emphasized in order that they may not lead to unwarranted conclusions. On the other hand, many of them can be depended upon to give valuable

and sometimes specific proof of glandular involvement. The description above will perhaps give the indications for each test and show in which conditions they will yield the most helpful information and thus give the indications for treatment.

Treatment.—Treatment of the various endocrine disorders has not been discussed in detail because it is obvious that efficient treatment can only be carried out when there is an accurate understanding of the pathologic condition under consideration. Methods of determining the diagnoses have been discussed in detail. In thyroid deficiency the main treatment depends upon the use of thyroid extract. In this connection it should be remembered that the different preparations of thyroid have different therapeutic strengths. For example, the corresponding dose of thyroid emplets of Parke, Davis and Company are approximately four times as strong as thyroid extract of Burroughs and Wellcome Company, and 3.3 grains of Parke, Davis' has the same therapeutic effect as 4.6 grains of Lilly's or Armour's thyroid. To date, it is difficult to differentiate between primary hypothyroidism and secondary hypothyroidism due to lack of the thyreogenic hormone of the pituitary. In a few of the cases of hypothyroidism, which do not progress to complete normality, the administration by mouth of various pituitary extracts has occasionally brought on greater improvement. To date no commercial preparation of the thyreogenic hormone is available which can be depended upon to be effective in these conditions.

A discussion of the treatment of hyperthyroidism cannot be gone into here. Although there is little question that surgical treatment is essential for most adults, it is my opinion that there are some cases in childhood which can well be treated medically and who respond to hygienic measures to the administration of iodine.

The treatment of parathyroid abnormalities requires very special knowledge and should be undertaken only by those who have laboratory facilities to control their treatment.

With the exception of undescended testicles, which respond very remarkably in a considerable proportion of the cases to antuitrin S, the various abnormalities of the pituitary are not yet clearly enough defined to be treated successfully without the use of expensive and technical investigations.

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CLINIC OF DR. JAMES MARVIN BATY

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FEEDING IN THE NEWBORN

THE first two weeks is a very important period in the baby's life—possibly the most important single two-week period in the entire life span. During this time the infant needs special care. He is becoming adjusted to living outside the mother and the bodily functions are assuming independent action. The digestive process is the one we are most concerned with since it is affected so much by factors over which the infant has relatively little control, and with which other individuals interfere. The perfection or imperfection of the other bodily functions is influenced to a much less degree by the care the infant receives. In spite of the fact that it is so important from the point of view of nutrition that infants be given interested, intelligent care during the newborn period, they are probably neglected more at this time than at any other. To be sure, this condition has improved greatly, but there is still need for betterment in the methods of handling babies in the neonatal period.

Broadly, there are two reasons why medical supervision is not so efficient during the newborn period as during later infancy. First, the baby naturally obtains a very small amount of food from the breast during the initial three days of life and frequently an inadequate supply for two weeks. Because of this and other reasons, the infant normally loses weight for three days after birth (approximately 10 per cent of the initial weight) and does not regain this lost weight until about ten to fourteen days postpartum. Insufficient attention therefore is apt to be given to loss of weight during the first few days, and there is always the danger that it will progress too far,

resulting in loss of vigor. It is in such instances that dehydration and "inanition fever" occur. If an infant is not gaining approximately 1 ounce a day after the fourth day he is actually losing ground, in that his weight is not keeping pace with his normal growth. Even though the weight is being maintained, such infants are apt to become less vigorous, more apathetic and nurse less well. The "lazy" poor feeders are usually babies of this type.

The second reason for the failure to provide optimum medical care during the newborn period has to do with the nature of medical practice. The pediatrician is the one physician who is most concerned with infant care, both from the point of view of interest and training. For various reasons, however, relatively few infants are seen by the pediatrician during the first few days of life. The exceptions to this rule are the large lying-in hospitals where a pediatrician is in attendance in the nursery and supervises the care of the babies from birth. The obstetrician is a highly specialized surgeon whose primary interests are rightly the mother and a successful delivery. Once the delivery is accomplished and the infant has begun to breathe normally, the obstetrician focuses his attention on the mother, leaving the baby to the care of the nurse or to some nursery routine. It must be granted that these routines are successful at least partially in the majority of instances, but relatively little attention is paid to the individual nutritional problems during this very critical period. As a result digestive disturbances occur. Even though these upsets are not severe they make the subsequent nutritional course more difficult than if they had not happened. A large percentage of infants, particularly in localities away from the larger medical centers, are delivered by the family physician who supervises the care of the infant as well as the mother. Theoretically this should result in ideal medical care for both patients. Entirely too often, however, the physician is engaged with a busy practice, has little time for or interest in the detailed care of the infant, and again the baby is left to attendants or formulae are prescribed which are based on tables supplied by detail men from proprietary food houses.

Any discussion of infant feeding must begin with the method provided by nature. The natural food for the human

offspring is its own mother's breast milk. If proof were needed to prove the truth of this simple axiom it is abundantly supplied by the fact that feeding difficulties are practically unknown during the early months of life in infants who are entirely breast fed. On the other hand such difficulties are relatively common with artificially fed babies. Many of these disturbances are of minor import, to be sure, but they must be handled carefully and intelligently because of the constant danger of their increasing to severity.

The important characteristics of breast milk may be briefly summarized. In the first place, the infant receives the food directly from its mother, without intervening handling, and it is therefore fresh and uncontaminated. When coagulation takes place in the stomach, fine, soft, flocculent curds are formed which are readily permeable to digestive juices. Secondly, breast milk contains all the food elements which are essential to growth and development in ideal proportions both as to quality and quantity. Fat, protein, lactose, mineral salts and vitamins are all present in adequate amounts.

Full lactation does not become established until the third or fourth day postpartum. During the latter months of pregnancy and the first few days after delivery the breast contains a secretion known as colostrum. This liquid is thicker than breast milk, has a higher specific gravity and is lemon yellow in color. The composition of colostrum varies considerably. It differs from breast milk chiefly in having a much higher content of protein and mineral salts. It has no proved important function for the newly born infant except that it supplies a small amount of food and fluid while the milk is coming in.

The infant should be put to the breast for the first time after an interval of twelve to twenty-four hours following birth, allowing both the mother and the child a period of rest after the ordeal they have just passed through. Some infants take hold and suck vigorously at the first contact with the breast, but the majority do not. Considerable help and patience are necessary since the procedure is novel to the primiparous mother as well as to the baby. The infant's mouth should be opened by gentle downward traction on the chin, and the nipple flattened between the fingers and thumb, placed between

the lips. Squeezing a little colostrum into the mouth may help to stimulate the sucking reflex. The infant must also be kept awake by gentle shaking, tapping the sole of the foot or by the application of a cold cloth to the face. The procedure should not be prolonged over ten minutes or so the first few times if the baby does not take hold, as nothing is accomplished, and the mother may become upset by such futile efforts.

During the twenty-four hours after the first nursing the baby should be taken to breast at intervals of about six hours; then on the third day postpartum the regular schedule of nursing should be established. The most practical schedule is to send the infant to breast at four-hour intervals for 5 feedings, replacing the sixth feeding at 2 A. M. with a supplemental formula feeding. The choice of formulae will be discussed later. This schedule is certainly the best possible for the mother as it allows her a reasonable interval between nursings, and an uninterrupted period of sleep at night. And, since the majority of infants thrive on such a schedule, it is equally ideal for the baby. It may be necessary, however, in rare instances to shorten the interval between feedings and to increase the number of feedings in the twenty-four hours to 7 or even more rarely to 8.

The question of prelacteal feeding naturally arises at this point. There has been considerable discussion, and there is still no agreement among clinicians, as to whether newborn infants should be fed anything during the first few days. Experiments have been carried out carefully on large numbers of babies in efforts to demonstrate the effectiveness of various types of feeding during this period. It is generally agreed that the initial loss of weight cannot be prevented entirely. It is also agreed that the amount of weight lost can be lessened appreciably by feeding from shortly after birth. Infants fed during the first few days of life on so-called "hydrating solutions," such as the gelatin solution recommended by Kugel-mass, or a sugar solution containing sodium citrate as used by Eder, do lose less weight. They regain their birth weight in a shorter period of time and they are said to be more vigorous than infants given no prelacteal feeding. However, since such solutions accomplish these effects by producing tissue hydra-

tion, they should be used very carefully if at all because of a tendency of infants taking them to develop edema.

A more reasonable procedure is to give water freely or a simple sugar solution, such as 5 per cent lactose or betalactose. Two to 3 ounces of such liquid should be offered every four hours beginning twelve hours postpartum, and as complement to breast feedings until lactation is fully established. Although these solutions do not affect the weight to the same degree as the hydrating solutions mentioned above, they do serve to lessen the initial weight loss and prevent the development of inanition fever. And, of course, edema is not apt to occur.

When the mother has an abundance of easy flowing milk and the infant sucks vigorously, it may be assumed that lactation is established satisfactorily, and complementary feeding may be omitted. If, however, the baby is not gaining in weight after the fourth day, and is otherwise normal, it is obvious that he is not getting enough at the breast and should be given more to eat. Breast milk, when available, either through use of the breast pump after the infant has nursed, or from some other source, is the food of choice. If breast milk is not obtainable, artificial food should be given in the form of a suitable complementary formula.

There is a very popular conception that a newborn infant will prefer the bottle to the breast if complementary feeding is attempted and that as a result there is less and less stimulation to the breast, with consequent drying up of the milk. It is therefore reasoned that the infant should be "starved into nursing." This idea is entirely erroneous. The baby will take milk from the breast at this age if he is able to get it. The breast feedings with complementary formula should be continued for at least ten or twelve days in an effort to establish adequate lactation. If, after a reasonable trial period, the infant is getting a negligible amount of milk from the breast, it is futile to continue. The baby should be weaned to an adequate formula.

In multiparous mothers the history of breast-milk production in previous pregnancies is important and helpful. If the mother has successfully nursed other babies she will probably be able to do so again. And conversely, if she was unable after a reasonable trial to nurse a previous infant, she will not have

enough milk to nurse others, and it is to the advantage of the mother and the baby to abandon the effort immediately in favor of artificial feeding.

There should be no rule of thumb in prescribing the artificial food for infants of any age, and there should be no exception to this rule during the newborn period. All efforts in the artificial feeding of infants are toward modifying the milk of a different species so that it can be digested by the human infant. For obvious reasons the milk of the cow is almost universally used in this country. But it must be remembered always that nature supplies cow's milk for the calf and that in the fresh state it is very indigestible and must be modified to meet the digestive abilities of the individual infant. The differences between breast milk and cow's milk and the various methods of modification of cow's milk for use in infant feeding are given in detail in all standard textbooks of pediatrics. For the purposes of this discussion it is sufficient to say that cow's milk contains approximately three times as much protein and one half as much sugar as breast milk; the proportional representation of the fats, proteins and salts differs in the two milks; and in the stomach cow's milk forms large, tough, indigestible curds, and because of a higher buffer value, neutralizes the acids of the gastric juices more rapidly. The methods for modification of cow's milk to increase its digestibility which are used today are boiling, evaporating, drying and acidifying. They each attain the same result and any one may be used successfully in artificial feeding during the newborn period as well as in later infancy.

There is a much broader understanding of the principles of infant feeding among physicians of today than existed even a few years ago. Certainly these principles are much simpler whether or not they are more scientific. The most important single factor responsible for the improvement in infant nutrition is the vastly better milk supply available for artificial feeding. The development of this cleaner, safer and more nutritious milk for general consumption has been made possible largely through the efforts of the producers of certified milk. The standards for this milk have been steadily raised. The result is commercial competition in the production of purer milk of all grades. The dairies producing certified milk are now under

the supervision of the American Association of Medical Milk Commissions. The requirements for certified and the other grades of milk sold on the Boston market are given in the tabulation.

TABULATION

Legal Standards for Certified, Grade A, Market Milk

Effective—September 1, 1925—Boston, Mass.

GRADE	*Bacteria Count (Not to Exceed)		Better Fat Not Less Than	Max. Age Before Pasteurization	Cow T. B. Tested	Cow Tested for Br. Abortus	Medical Supervision of Employee	Bottled and Sealed at the Farm
Certified Milk Raw or Pasteurized	10,000	500	4%	24 hrs.	Yes at least twice yearly	Yes	Yes at least weekly	Yes
Grade A Milk Pasteurized	100,000	10,000	4%	48 hrs.	Yes at least every 3 years	No	No	No
Market Milk Pasteurized	400,000	40,000	3.35%	72 hrs.	Yes at least every 3 years	No	No	No

All milk sold in Boston must be pasteurized, excepting only milk Certified by the Medical Milk Commission of Boston, Inc., which may be sold raw as Certified Milk Raw, or pasteurized as Certified Milk Pasteurized.

*Standard plate count of bacteria in one cubic centimeter.

The routine for artificial feeding of the newborn infant should approximate closely that outlined above for breast feeding. The baby is given nothing until twelve hours after birth, when 3 ounces of water or a simple sugar solution are offered, and every four hours thereafter until twenty-four to thirty-six hours of age. The same amount of a suitable formula is then substituted for the fluid. The infant should be allowed to take what he will of this without forcing. The amount ingested during the first few days varies from $\frac{1}{2}$ ounce up at each feeding, rarely as much as the 3 ounces offered.

It is even more important to adhere to a four-hour schedule in artificial feeding since the emptying time of the stomach is slower following the ingestion of cow's milk than it is after taking breast milk. Very rarely, in small or feeble infants who will take only 1 ounce or so at a time it is advisable to shorten the interval between feedings to three or even two hours.

If a dilution of cow's milk is to be used in the preparation of the formula, which requires 18 ounces for the twenty-four-hour period, 9 to 12 ounces of milk should be diluted with 9 to 6 ounces of water and boiled three to five minutes. One-

half to 1 ounce of a sugar, such as lactose, or a dextrin-maltose preparation, completes the formula. It is not necessary to dilute the milk more than one half, but it should be diluted at least one third. The kind of sugar used is of very little importance to the normal infant. Lactose as the natural sugar of milk would seem to be the most logical. However, other sugars work just as well, particularly cane sugar and the dextrin-maltose preparations, several of which are on the market.

The safest procedure in the routine feeding of newborn infants is to begin with the weaker dilution of milk and after two or three days increase the amount of milk and of sugar in the formula. There is relatively little danger of overfeeding at this time if the formula used is not too strong. It is not necessary to compute the caloric or protein requirement of the infant as a basis for the formula as the full caloric requirement will not be taken until at about the end of the first week. At this time the formula should have approximately the same caloric value as that of breast milk, 20 calories per ounce. Such a formula would be: whole milk, 12 ounces; water 5 ounces; sugar, 1 ounce. During the second week the average infant weighing above 5 pounds at birth will take about $2\frac{1}{2}$ ounces per pound of body weight of this formula in the twenty-four-hour period.

If the infant shows evidence of indigestion such as failure to gain accompanied by vomiting, or persistently abnormal stools, the formula should be omitted, fluids again administered by mouth and parenterally if necessary, for a period of twelve to twenty-four hours, before again giving a formula or preferably breast milk. Minor degrees of indigestion which require no change in régime are much more common and are merely evidences of difficulties on the part of the intestinal tract to becoming adjusted to a foreign food.

Vomiting deserves special comment because of its common occurrence during the newborn period. Infants frequently vomit several times the first two days of life, apparently because of accumulated mucus and swallowed amniotic sac contents in the stomach. The vomiting may be due in part at least to concussion of the brain associated with the trauma of birth. Treatment is not necessary in the majority of instances. Occasionally when vomiting is persistent, the stomach may be

lavaged with a weak sodium bicarbonate solution. Continuation of the throwing up following this procedure suggests some underlying cause such as an anomaly of the gastro-intestinal tract or a cerebral hemorrhage.

No effort has been made to discuss all of the various modifications of cow's milk available for the artificial feeding of infants. Every physician is to some degree familiar with the various evaporated milks, acid milks, reconstructed milks and dried milks that are on the market through the advertisements of their several manufacturers. Each of these products that has been accepted by the Council of the American Medical Association is a well balanced food, and may be used satisfactorily in feeding babies. In fact, there is evidence that many of them are more digestible and therefore preferable to the simple boiled milk dilution outlined above, which has been satisfactory in our clinics. As long as the general principles of infant feeding are adhered to, whether the milk is fresh, evaporated or dried is not so important as the behavior of the individual infant being fed.

CLINIC OF DR. RICHARD M. SMITH

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THE MANAGEMENT OF NUTRITIONAL DISORDERS OF INFANCY

WE might begin this discussion with a definition of what we mean by "nutritional disorders." Since infants do not express their subjective sensations in readily understandable language, we must depend upon objective signs for the recognition of disease conditions. Nutritional disorders are made manifest in most instances by 1 of 3 symptoms occurring singly or in combination. These 3 symptoms are: modifications in the normal gain in weight; stationary weight or loss in weight; vomiting, and diarrhea. Out of 3000 consecutive admissions to the Infants' Hospital, Johnson found that 75 per cent of the babies were brought to the hospital because of one of these complaints. One is impressed in these figures with the importance of nutritional disorders in the practice of any physician who is concerned with the care of infants.

It is encouraging to note the steady but striking reduction in the deaths of infants from diseases of the gastro-intestinal tract. In Massachusetts in 1900, 157 infants under one year of age died from all causes per every 1000 live births; in 1936 the corresponding figure was 47. Most of this saving of infant life has been due to the reduction of deaths from the gastro-intestinal diseases. In 1900 nearly 29 per cent of the infant deaths were due to these diseases—in 1936 only 5 per cent. If the 1900 death rate had obtained last year there would have been 2600 more infant deaths in Massachusetts than actually did occur. Similar figures could be presented from other states and from the United States as a whole.

There are 2 factors which are responsible for this gratifying saving of infant life. There has been a definite reduction in the number of severely ill infants due to the widespread use of

sion of effective preventive measures, and the infants who are ill receive better treatment. Anyone whose medical experience extends backward for twenty years or more is conscious of the virtual disappearance of the severe type of illness in infants which occurred primarily in the summer months. Not only does one seldom see these severely ill infants but the seasonal distribution has largely vanished. The preventive measures which are chiefly responsible for this altered situation may be distinguished but their relative importance cannot be evaluated. They are 3 in number: a better understanding of the nutritional requirements of infants, the pasteurization of milk, and the education of mothers in the care of their babies. It is not possible in the time allotted to this clinic to consider these matters and to indicate how they have been effective in preventing disease. We shall confine ourselves to a discussion of the care of those infants who become ill despite these preventive measures.

In the care of any infant ill with a nutritional disorder, our first concern should be to determine the etiology of the condition. In our experience, the causes may be grouped under 4 main headings and in the following order of frequency: infection, congenital anomalies, environment or hygiene, and food. In attempting to make a diagnosis of the underlying cause, a careful history is essential. This should include information as to the exact food the infant has been taking and the progress of symptoms from the onset of the illness. Time relationship may have great significance, especially in estimating the rôle of congenital anomalies. A complete physical examination must be made. This should be an unnecessary point to stress, yet one finds a cursory examination not infrequent. The exact condition of the infant forms the basis upon which both diagnosis and adequate treatment depend.

Infection is the commonest cause of nutritional disorders in infants. It is to be remembered that infants frequently do not respond to infection by an elevation in temperature. They may go through the whole course of a severe infection with rectal temperature readings not above 99.2° or 99.6° F. There is usually a polynuclear leukocytosis, perhaps evident only by a change in the relative proportion of neutrophils, but a normal blood picture may be found. Probably the most common in-

fection causing a nutritional disorder is in the respiratory tract. The history frequently fails to indicate any evidence of such infection and the physical examination may be negative except for slight signs, the significance of which may not be appreciated. A slight injection of throat, pink ear drums, modification in the cry, and a little nasal discharge may be all that is found. Infection in the body elsewhere than the respiratory tract also may give slight physical signs. Meningitis may occur without a stiff neck or abnormal reflexes and a lumbar puncture may be necessary to confirm the diagnosis.

Congenital anomalies must always be considered as playing a possible etiologic rôle in connection with any disease in infants. Anomalies of the gastro-intestinal tract are not uncommon and may cause symptoms not only early in infancy but throughout the period of childhood. Anomalies in other parts of the body may cause gastro-intestinal symptoms, especially if there is a superimposed infection. This is seen particularly in anomalies of the urinary tract with pyuria.

Environmental factors which form the basis for nutritional disorders are less evident than formerly. Summer diarrhea has largely disappeared. The possible influence of climatic conditions is, however, not to be entirely ignored. The routine technics of care may be so erroneous as to precipitate serious disease. Too much handling, overstimulation, and irregular habits are often found as exciting causes of disturbed nutrition.

You will notice that food is fourth in the list of the underlying causes of nutritional disorders. Cure is not likely to result from the simple device of changing the content of the diet. It is, perhaps, a natural first reaction to assume that some error in feeding is responsible for the illness. Due to the factors already mentioned, gross errors in the feeding of infants occur surprisingly infrequently. There is a marked variation in medical practice in the application to individual infants of the known principles of nutritional requirements but within these variations there is provided the dietary needs of most infants. If a nutritional disorder develops in an infant who is under good medical supervision, the cause is usually found to be something other than improper food.

The treatment of the precipitating cause of the nutritional disorder should be given first thought but therapeutic pro-

cedures directed toward its relief should not necessarily be instituted at once. This treatment will, of course, vary with the cause. If a congenital anomaly is present, surgical intervention may be indicated but if possible should be postponed until the nutritional disorder is improved or cured. If the infection can be treated by a specific therapeutic measure, it should be instituted at once. If some procedure such as myringotomy is indicated, it should be done. The infection may be one in which no specific treatment is possible and then one must rely upon general measures and a relief of symptoms.

The nutritional disorder itself requires consideration even though it has arisen secondarily to some primary disease. This may be of a relatively mild character. If so, the withholding of fluid by mouth for a few hours, followed by a period of restricted feeding may be all that is necessary. In many instances the vomiting and diarrhea has been so prolonged or so severe as to make the nutritional disorder of primary importance, requiring prompt and active treatment. The loss of fluid from the body causes dehydration with acidosis or alkalosis. This gives a typical clinical picture in infants. The fontanel is depressed, the eyes sunken, the abdomen scaphoid, the skin dry and inelastic. In order to treat this condition intelligently, it is necessary to understand something of the physiologic processes concerned with body fluids. Knowledge of this complicated subject has been clarified by the beautifully conducted experimental work of Gamble and his coworkers and by the investigations of Hartman and others.

Fluid is contained in 3 compartments in the body: the circulatory system, the intercellular spaces, and the body cells. It enters the body by absorption from the small intestine. It leaves the body under normal conditions through the kidneys, lungs, skin, and in very small amounts from the gastro-intestinal tract. Body fluid contains water and electrolytes. In the blood plasma the electrolytes occur at a constant level of concentration for each separate electrolyte. These values are kept constant by the specific regulatory function of the kidney. This function is effective in the normal kidney so long as blood volume remains normal. Blood volume is maintained at a constant amount by replenishment from the supply of fluid in the other compartments of the body. The electrolytes

in the blood plasma consist of acid and base radicals, occurring in such balance that the reaction of the blood is constant. When the relative proportion of one radical is excessive there is either alkalosis or acidosis. The important basic radical in the blood plasma is sodium and the largest acid radical is the chloride ion. The other basic and acid electrolytes exist in such relatively small amounts that they need not be considered in this connection. The fluid in the intercellular spaces contains electrolytes of the same kind as in blood plasma and in essentially the same levels of concentration. In intracellular fluids the electrolytes are different, the basic ion is potassium, and the acid is phosphorus.

When vomiting and diarrhea occur, either one alone or both together, the usual supply of body fluids is reduced, first by failure to retain fluids taken in by mouth, and second by actual loss of water and electrolytes from vomiting of gastric secretions and from watery bowel discharges. It is to be noted that when there is either vomiting or diarrhea, fluid is being withdrawn from the body, often in large quantities, through channels which normally remove only a negligible amount. The chloride ion is most abundant in the gastric secretions so that when vomiting predominates there is an excessive loss of acid substances. The intestinal secretions have a high sodium content so that when diarrhea predominates there is an excessive loss of basic substances. In normal infants, the regulatory function of the kidney would remove the electrolytes present in excess in the blood plasma but when dehydration is present, kidney function is lowered and the electrolytes in the blood plasma cannot be restored to normal concentration. With excessive vomiting there is produced an alkalosis and with diarrhea, an acidosis.

The double drain upon body fluids from limitation of intake and expansion of output results in certain changes in the distribution of the fluid within the body. The first change is withdrawal from the intercellular spaces into the circulatory system of some of the fluid held there in reserve as a reservoir, the level of which can be raised or lowered as the demands of the body require. We do not know exactly how this mechanism of withdrawal is activated for there are many factors concerned. In addition to the necessity of keeping the electrolytes

in the blood plasma at constant levels of concentration, there is the influence of pressure within the blood vessels and also the permeability of the walls of cells to be considered. By some process normal blood volume is maintained until the reservoir of fluid in the intercellular spaces is exhausted. So long as blood volume is within normal limits, kidney function remains normal. If vomiting or diarrhea continues after the intercellular fluid is depleted or exhausted, the concentration of the electrolytes in the blood plasma increases but blood volume cannot be increased to restore them to normal relations. Because of the different electrolyte composition of intracellular fluid, it is not directly suitable as a further reservoir for maintaining blood volume. Probably some fluid is withdrawn from normal cells and some additional fluid is utilized from cells which are destroyed to furnish material to maintain the metabolic processes of the body during what is virtually a starvation period because of the absence of food taken by mouth. The intracellular fluid, if used to replace the electrolytes in the blood plasma, must be modified materially by the regulatory function of the kidney. We know that kidney function is lowered in the presence of decreased blood volume. Thus a vicious circle is established which adds still further to the disordered nutrition. The actual values of the various substances in the blood of any particular infant can be determined by appropriate measurement.

The treatment of dehydration is directed toward supplying to the body the water and electrolytes which have been lost so that normal blood volume is restored and normal kidney function reestablished. Physiologic salt solution which contains both sodium and chloride supplies the needed electrolytes in a fluid medium. When given into the tissues, *i. e.*, into the intercellular space, it is available for absorption into the circulating blood. The regulatory action of the kidney eliminates the excess of chloride in relation to sodium. Blood plasma and blood volume again return to normal values.

If dehydration is severe, physiologic salt given by hypodermoclysis is absorbed slowly and may be inadequate to reestablish kidney function. Until kidney function is established the dehydration cannot be relieved. It is necessary to introduce fluid directly into the circulatory blood. Ten per cent

glucose solution is a particularly effective fluid for this purpose. It increases the volume of the blood and by its hyper-tonic action hastens the absorption of the fluid introduced into the intercellular space. It furnishes water immediately available for excretion by the kidneys. It also causes the ketone bodies to disappear from the blood if they are present.

In severe dehydration with acidosis the concentration of sodium bicarbonate in the blood plasma may be so reduced that the restoration to normal values is too slow when physiologic salt alone is relied upon. In such circumstances sodium bicarbonate may be given intravenously or, better, sodium lactate added to the sodium chloride solution which is given subcutaneously. After absorption, the lactate is oxidized and sodium bicarbonate formed. The mixture for such a purpose used subcutaneously is prepared with 6 parts of isotonic sodium lactate solution and 4 parts of physiologic salt solution. This solution should not be used when there is alkalosis.

In addition to the subcutaneous introduction of physiologic salt solution with or without sodium lactate and the intravenous administration of 10 per cent glucose solution, another therapeutic procedure is often of value in the treatment of dehydration. Transfusion with whole blood from a suitable donor increases blood volume and also furnishes the substances needed to restore the blood plasma to the normal concentrations.

The quantities of the various fluids to be used depends upon the weight of the infant. Subcutaneous fluids may be given from 10 to 15 cc. and intravenous glucose solution from 5 to 10 cc. per pound. Transfusion of whole blood should not exceed 10 cc. per pound. Treatments with subcutaneous and intravenous solutions may be repeated every eight or twelve hours as the condition of the infant indicates. In very ill infants it may be desirable to administer fluids continuously into the veins. This procedure is adopted when the response to other treatments is unsatisfactory, when vomiting and diarrhea persist, or when the severity of the dehydration indicates the need for more active measures. The solution used for continuous intravenous therapy is composed of equal parts of 10 per cent glucose and lactate-saline solutions. The lactate-saline solution is made of 2 parts physiologic salt solution and

1 part isotonic sodium lactate solution. It should be given slowly, by drops, the exact rate depending upon the fluid requirement of the infant—2 to 3 ounces per pound per day. When this treatment is used, care must be taken that the infant is not overhydrated—as shown by edema and low serum protein in the blood.

The case histories of 2 infants illustrate the practical application of the principles which have been discussed. A six-weeks-old infant was admitted to the hospital with pyloric stenosis with a history of vomiting for two weeks. There were no other significant facts in the history. The physical examination showed the typical signs of the condition and, in addition, marked malnutrition and dehydration. The chemical examination of the blood showed sodium 138 milliequivalents per liter, chlorides 66 milliequivalents per liter, serum protein 6.7 Gm. per cent, nonprotein nitrogen 43 mg. per cent and CO_2 112 volumes per cent. (There was a definite alkalosis.) The infant was given a clysis of 120 cc. of physiologic salt solution and 60 cc. of a 10 per cent glucose solution intravenously. This was repeated the same day and once the second day. After this treatment the blood chemistry was: sodium 118 milliequivalents per liter, chloride 78 milliequivalents per liter, serum protein 5.4 Gm. per cent, and CO_2 92 volumes per cent. She was transferred to the surgical service for operation.

A two-month-old female infant entered the hospital with a history of diarrhea, refusal of food, and loss of weight of two weeks' duration. The birth was normal. There were no post-natal disturbances. She was breast fed for two days only. Bottle feeding was adequate. No orange juice or cod liver oil had been given. Gain in weight was satisfactory. Two weeks before admission the stools became green and watery. One week later there was refusal of food and on several occasions when feeding was forced, there was vomiting. There had been considerable loss of weight but the mother did not know the exact amount. On examination the infant was drowsy and did not cry. The skin was dry and nonelastic. The fontanel was depressed. The left ear drum was red and retracted. In all other respects the examination was normal. The temperature was 99.2°F. , the weight 7 pounds and 12 ounces (birth weight).

8 pounds). The urine was negative except for a slight trace of albumin—no acetone was present. The white count was 28,800 with 51 per cent polynuclears. The hemoglobin was 15.29 Gm. and red cells 4,440,000. The blood chemistry was: sodium 135 milliequivalents per liter, chloride 112 milliequivalents per liter, nonprotein nitrogen 125 mg. per cent. As shown by the very high nonprotein nitrogen there is evidently a marked concentration of the blood and there is a relative acidosis. The underlying cause was probably a mild respiratory infection. The infant was given 120 cc. of lactate-sodium chloride solution subcutaneously and 80 cc. of equal parts of this solution and 10 per cent glucose solution intravenously. A continuous drip was started and allowed to run for six and one-half hours. At the end of that period 225 cc. had been administered. This was twelve hours after admission and the total fluid given had been 425 cc. The condition of the patient was improved. The next day the infant was transfused with 80 cc. of citrated whole blood. Another clysis and intravenous glucose solution was given. On the third day the white count had fallen to 10,000, the weight had increased to 9 pounds and 2 ounces. The vomiting and diarrhea had stopped. Progress was uneventful to recovery.

During the early stages in the treatment of dehydration, if vomiting is present no attempt should be made to give any food or fluid by mouth. After a few hours of starvation 1 drachm of fluid may be given every ten or fifteen minutes. If this is retained, the amount of fluid may be increased and the interval between feedings lengthened. This process should be gradual and not so rapid as to precipitate a return of the vomiting. A satisfactory fluid to use is made by mixing equal parts of physiologic salt solution and 10 per cent glucose solution. From what has been said it is obvious that this fluid is peculiarly adapted to assist in the restoration of body fluids to normal conditions. Other fluids—fruit juices, cereal water, and milk mixtures—are added as the condition of the infant indicates. No exact rules can be given. The physician must be guided by his own judgment and experience.

Summary.—The management of an infant with a nutritional disorder should proceed in general along these lines.

1. On the basis of a careful history and a complete phys-

ical examination an attempt should be made to determine the etiology of the disorder.

2. If the primary cause is a congenital anomaly, one must consider whether or not immediate surgical treatment is indicated. If an infection is found to be present, appropriate specific measures must be instituted or general measures if these are the only ones available. If environmental factors, hygiene, or food have been faulty, consideration must be given to preventing a recurrence of these causes after the existing disorder has been corrected.

3. The complications of the nutritional disorder may require immediate treatment. The most common and most urgent complication is dehydration with alkalosis or acidosis and an accompanying failure in kidney function.

4. Dehydration is treated by the subcutaneous injection of physiologic salt solution with or without sodium lactate, the intravenous administration of 10 per cent glucose solution, and in severely ill infants, transfusion with whole blood.

5. No fluids should be given by mouth for several hours if vomiting is severe. Saline and glucose solution is the first fluid to be used when feeding is resumed. Food and other fluids are added in gradually increasing amount as the progress of the infant toward recovery indicates.

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GONOCOCCAL ARTHRITIS

THE case I propose discussing today illustrates several features which are uncommon in patients with gonococcal arthritis. Before presenting the history of the illness, it is perhaps well to review some of the facts concerning the gonococcus, and the pathogenesis of the various disorders caused by this organism.

The gonococcus is a gram-negative diplococcus which causes infection only in man. All attempts to establish infection in animals have failed unless large numbers of organisms are injected into the circulating blood or peritoneal cavity. Even under these circumstances the results are irregular unless massive doses are used. Recently Long and Bliss¹ and Cohen² have reported the production of infection in mice using the mucin technic as recently described by Miller and Castles.³ They have found, in common with Miller,³ that in order to infect mice large numbers of organisms must be injected into the peritoneal cavity.

From many studies it is now known that there are numerous strains of gonococci which differ in their antigenic relationship. In general, it has been found that there are two main types but between these types there are a number of strains which have one or more antigenic components which are common in both main types.

Miller and Boor⁴ have demonstrated that the gonococcus contains both polysaccharide and nucleoprotein substances. The latter are shared in common by other members of the *Neisseria* group, as well as pneumococci. Recently Casper⁵ has been able to show that the carbohydrate fraction of the organism is responsible for type-specificity, where the nucleoprotein

fraction is nontype-specific and probably related to the protein fraction of other microorganisms.

From studies of Clark, Ferry and Steele,⁶ de Christmas⁷ and others it has been found that filtered broth cultures of gonococci contain substances which are histiotoxic when injected into the tissues of man and animals (horses). When this toxin is injected into horses an antitoxic immune serum can be developed which has neutralizing power. Whether this substance is a true exotoxin in the sense that it is a substance elaborated by the organism, or whether it is due in part to the autolysis of organisms, is a matter difficult to decide. Certainly the antiserum elaborated by the injection of toxic filtrate will neutralize the toxin when it is injected into the skin of man but it is not bactericidal. In any event the products of the gonococcus are histiotoxic and may explain many of the phenomena of such infections.

IMMUNE BODIES IN GONOCOCCAL INFECTION

Following infection with gonococci, bacteriolysin and complement-fixation antibodies may be demonstrated in the circulating blood. Normal, noninfected individuals often have bacteriolysins in their blood for some strains of gonococci. Spink and I⁸ have shown that these antibodies are more often present against strains that produce a local lesion, than against those which produce arthritis. It is also evident that during and following infection with the gonococcus, antibodies develop in the circulating blood in increasing titer. When there is bacteremia no antibodies can be detected in the blood. When recovery occurs in such individuals, antibodies appear. From a limited number of studies it seems clear that recovery following bacteremia due to gonococcus is accompanied by the development of specific antibodies and a clearing of the blood stream. This can be accomplished in some cases following the injection of specific immune sera.⁹

When the synovial fluid is studied for antibodies in patients with gonococcal arthritis, it can be shown that when the fluid is infected no antibodies are demonstrable. When the fluid is sterile, antibodies are present in a high percentage of cases. When the antibody content of the blood and the synovial fluid from the same individual are compared, it is seen that in patients with infected synovial fluid the titer of the bacterial

antibodies of the blood is low. When the fluid is sterile, the bactericidal action of both the blood and synovial fluid is either the same, or the blood may contain a titer of antibody that is higher than that of the synovial fluid. There are occasional instances in which the bactericidal titer of both the blood and synovial fluid is low in spite of the fact that the synovial fluid remains sterile. There are reasons for believing, then, that one of the mechanisms by which the synovial fluid is sterilized in gonococcal arthritis is the development of specific bactericidal antibodies.

PATHOGENESIS OF GONOCOCCAL INFECTION

In the vast majority of cases of gonococcal infection the inflammatory process is confined to a localized area, such as the urethra, the conjunctiva, the uterine cervix, the vaginal

TABULATION

Local Infections

1. Urethra
2. Conjunctivae
3. Vulvovaginitis in children
4. Cervix uteri
5. Rectum

Infections Arising by Direct Extension from a Local Focus

1. Posterior urethritis
2. Prostatitis
3. Epididymitis
4. Seminal vesiculitis
5. Salpingitis
6. Peritonitis—Pelvic
Subdiaphragmatic
7. Pyelitis and cystitis

Infections Occurring as Metastases from Bacteremia or Toxic Products of the Gonococcus

- | | |
|--------|--|
| Common | <ol style="list-style-type: none"> 1. Arthritis 2. Tenosynovitis 3. Conjunctivitis 4. Iritis—iridocyclitis |
| Rare | <ol style="list-style-type: none"> 5. Endocarditis 6. Keratoderma blenorrhagica 7. Vesiculopustular eruption 8. Acute nephritis 9. Meningitis 10. Myelitis 11. Periostitis 12. Exostoses 13. Perichondritis of ears, ribs, larynx 14. Thrombophlebitis 15. Liver abscess 16. Pleurisy—pericarditis |

epithelium in children, and the rectum. From these areas, however, the infectious process may spread by direct extension, by the lymphatics, or by way of the blood stream. The various pathologic lesions that may be produced following a local infection are listed in the Tabulation, and it is evident that a wide variety of lesions may follow this infection. With these facts in mind, we may now proceed to the presentation of the case.

A WOMAN WITH GONOCOCCAL INFECTION OF THE CERVIX UTERI DEVELOPS CHILLS, FEVER, ACUTE ARTHRITIS, SUPPURATIVE POLYARTHRITIS, TENOSYNOVITIS, GONOCOCCAL BACTEREMIA AND ASEPTIC MENINGITIS. RECOVERY FOLLOWS AN ILLNESS OF THREE MONTHS' DURATION

A thirty-four-year-old white woman enters the hospital complaining of pain in the chest and joints. Seven days before admission there was a sudden onset of illness with a shaking chill, malaise, and weakness. The following day her throat was sore and the chills and fever were repeated. Two days later she complained of severe pain in the right shoulder and left ankle. All of the aforementioned symptoms continued and increased in severity until the day of admission when she complained of pain in the back of the neck and a constant, dull headache. There was complete anorexia and vomiting two or three times daily.

The family and past histories were unimportant except for the fact that she had been separated from her husband for a period of three months.

Examination showed an obese white woman who was acutely ill. Temperature was 102.6° F., pulse 112 per minute respirations 28 per minute, blood pressure 145 systolic and 105 diastolic. The tonsils were moderately enlarged and injected. There were a few tender glands at the angle of the jaw, slight stiffness of the neck, and a few râles over the lung bases with many rhonchi. The heart was not enlarged and there were no murmurs. The abdomen was negative. There were all the signs of an acute arthritis of the right shoulder and right acromioclavicular joint. There was an acute arthritis of the left ankle joint and a tenosynovitis. Vaginal examination showed a purulent discharge. The reflexes were normal.

Laboratory examination showed the red blood cell count was 4,770,000, hemoglobin 74 per cent, white blood cell count 15,300 with 87 per cent polymorphonuclear leukocytes. There were no abnormal leukocytes seen. Smears and cultures of the cervix uteri showed numerous gonococci. The gonococcal complement-fixation test was positive. The blood culture was positive for gonococci. Lumbar puncture showed spinal fluid—initial pressure 360, 389 lymphocytes, 47 polymorphonuclears; total protein was 38 mg.; sugar 34 mg.; chlorides 717 mg. x-Ray examination of the left foot and right shoulder showed no bony changes but soft tissue swelling.

Course of the Disease.—The patient was under observation for a period of one hundred eight days. During the first month her temperature ranged from 99° to 101° and 103° F. daily. During the first week of observation the signs of meningitis gradually diminished and the spinal fluid became normal. The last examination showed an initial pressure of 240 with 5 lymphocytes and a normal chemical pattern. At the end of the first week gonococci were grown from the circulating blood, and aspiration of the right shoulder joint and left ankle showed gonococci on culture. In view of the positive blood culture she was given 5 cc. of antigonococcic horse serum (Parke-Davis) intravenously, but since this was followed by a rather sharp febrile reaction she was given an additional 20 cc. of serum intramuscularly several hours later without any untoward effect. Following this treatment 7 additional blood cultures, taken at one-week intervals, were negative. During the fourth week of observation an area of fluctuation appeared over the right foot, especially in the tendon sheath of the large toe. Aspiration of material from this suppurating tendon sheath revealed gonococci. Following drainage of this abscess and the local applications of heat, the discharge stopped and there was complete healing. The fever persisted between 100° and 101° F. for ten weeks. It gradually declined and reached a normal level at the end of twelve weeks. The arthritis gradually improved but she had definite permanent limitation of motion in the right shoulder joint; the left ankle also remained stiff and was limited in its range of motion. She was discharged from the hospital with a diagnosis of gonococcal

urethritis and cervicitis, arthritis, tenosynovitis, and aseptic meningitis.

Comment.—This patient showed a number of most interesting features of gonococcal infection. When she was first observed, it was thought that the acute arthritis was due to the preceding respiratory infection. However, the presence of gonococci in the vaginal discharge, the blood, and the material obtained from the tendon sheath with the positive complement fixation reaction removed all doubt concerning the etiologic diagnosis.

The factors I should like to discuss are the bacteremia, the suppurative tenosynovitis, and the aseptic meningitis.

Bacteremia due to the gonococcus is not often demonstrable, although it must occur as a transitory phenomena not infrequently. It has been observed most often when there is a vegetative endocarditis, but as in the present case it is occasionally seen during the course of a pelvic infection with metastases. Spink and I have observed several cases with bacteremia⁹ and it was apparent that during the blood invasion there were no antibodies present in the circulating blood but as recovery occurred, or following the exhibition of immune serum, antibodies appeared in the blood and the bacteremia disappeared. When endocarditis is not present in cases with bacteremia, the prognosis is not so grave as in those with endocarditis. The analysis of the reported cases of gonococcal septicemia by Bakst, Foley and Lamb¹⁰ shows that the fatality rate is 93 per cent in cases with endocardial damage. In the patients without endocardial disease recovery occurs more frequently.

In any case of bacteremia, then, the heart should be examined carefully for signs of endocarditis and a thorough search should be made for other foci of infection which might be treated, and immune serum should be given in an attempt to clear the blood stream.

While tenosynovitis is very common in gonococcal infection, it is rarely suppurative as in the present case. Suppurative gonococcic tenosynovitis has been made the subject of a special report by Birnbaum and Callander¹¹ who report 2 cases and review the literature. They emphasize the fact that the clinical manifestations are similar to those resulting from the

common pyogenic organisms except for the fact that the tendon itself is not usually destroyed. The diagnosis can be made with certainty only when the gonococcus is found in the exudate.

Gonococcus meningitis is exceedingly rare and Steiner¹² has recently collected 9 cases from the literature and added another case. The meningitis followed urethritis, arthritis, ophthalmitis, vulvovaginitis, and endocarditis, and 7 out of 10 cases recovered. These cases fulfilled the criteria of demonstrating gonococci by smear and culture of the spinal fluid, and by the fermentation of dextrose. More recently Branham, Mitchell and Brainin¹³ have reported an additional case which recovered following prontosil (sulfanilamide) treatment, and they state that they have studied 3 strains of gonococci which have been isolated from the spinal fluid.

In the present case there were clinical signs of meningitis and the spinal fluid confirmed the diagnosis. However, we were unable to cultivate the organism from the fluid and it was clear with only a moderate increase in the number of cells. I think that the important fact to remember in this connection is that meningitis occasionally occurs as a complication of gonococcal infection, and that the prognosis is reasonably good.

Aside from the bacteremia, tenosynovitis, and aseptic meningitis, this patient had arthritis. This feature of gonococcal infection is common and requires discussion. I propose, therefore, to say something concerning the diagnosis of gonococcal arthritis and then discuss its differential diagnosis.

DIAGNOSIS OF GONOCOCCAL ARTHRITIS

The diagnosis of gonococcal arthritis depends upon: (1) the history or the presence of a recent attack of gonorrheal infection; (2) the clinical features and course of this disease; (3) the isolation of gonococci from a local lesion and synovial fluid; (4) the presence of a positive gonococcal complement-fixation test.

The history of a recent or previous attack of gonorrhea is most often obtained in male patients. It is well recognized that in women there may be no history suggesting gonococcal infection of the genitalia, but in such instances recurrent attacks of pelvic pains or pain in the right upper quadrant,

coming on especially with or before the catamenia, are important points in the history. The attacks of pain in the lower quadrants are due to salpingitis or pelvic peritonitis, whereas the pain in the right upper quadrant is commonly the result of perihepatitis. In some individuals such attacks may clear up and the arthritis follows. Spink and I¹⁴ have reported cases in which the original focus of infection was either latent or had healed and organisms could be isolated from the synovial fluid. In most instances the arthritis developed within a period of from two to three weeks following the initial infection. However, we have observed patients in whom arthritis did not appear for at least four to six weeks after the initial infection. In one patient we noted a relapse of arthritis with an infected fluid several years after an attack of urethritis, and at the time of observation no evidence of a genital gonococcal infection could be elicited. It is obvious, then, that a negative history, especially in women, is of little value in excluding gonococcal arthritis.

CLINICAL FEATURES OF GONOCOCCAL ARTHRITIS

The clinical features of gonococcal arthritis, when considered with other lesions, are often of the the greatest importance in diagnosis. As a rule, the onset is insidious with multiple arthritis which may be mild or severe in character. This often coincides with a sensation of acute symptoms of urethritis or following an extension of the infection from the anterior urethra to adjacent organs. Not infrequently it follows vigorous local treatment. The pains in the joints may be transitory and subside completely. More commonly, however, one or more joints remain painful. The symptoms and signs of acute synovitis, with or without a tenosynovitis, become exaggerated until there is unmistakable evidence of an acute inflammation. Accompanying the arthritis there is fever and leukocytosis of indeterminate duration, although in many cases the temperature returns to normal and the joint pains continue. The joints show periarticular swelling, and the tendon sheaths are involved either alone or with the synovial membrane of the joints. This is seen very frequently and is of considerable diagnostic significance. The failure of the symptoms and signs of acute arthritis to subside promptly fol-

lowing the administration of salicylates and the persistence of the pain without fever should always arouse one's suspicion of a gonococcal infection. Such associated lesions as bilateral metastatic conjunctivitis or other metastatic lesions due to gonococci also aid in establishing the diagnosis. Whenever one's suspicions are aroused a search should be made for a local focus of infection. The joints should be aspirated in order to determine whether or not gonococci are present, and gonococcal complement-fixation tests should be done.

ISOLATION OF GONOCOCCUS FROM LOCAL LESION AND SYNOVIAL FLUID

It is now well established that culturing the organisms from a local focus is much more accurate and a better method of diagnosis than the use of simple smears and the staining of exudate. For this reason, all suspicious exudates should be cultured on suitable media. In the case of synovial fluid only about 30 per cent of cases have infected fluid; the remainder are sterile. It has been shown that the reason for the sterile synovial fluid in most cases is due to the presence of specific antibodies. In certain cases one may be able to isolate the gonococcus from the synovial fluid when it is not found in a local focus of infection in the genitalia. For this reason, all synovial exudates should be aspirated and cultured. In the cases in which the synovial fluid is sterile, the diagnosis usually depends upon finding a local focus of infection, commonly in the genitalia, the associated features of the disease and clinical course, and the gonococcal complement-fixation test.

GONOCOCCAL COMPLEMENT-FIXATION TEST

In our experience the gonococcal complement-fixation test is positive in approximately 85 per cent of cases of gonococcal arthritis. It usually becomes positive within two weeks after the onset of the arthritis and may remain positive for as long as six months to a year after the infection has become established. In brief, then, the diagnosis of gonococcal arthritis is usually based upon the history, demonstration of an acute or chronic primary gonococcal infection, the character of the lesions in the joints, the course of the disease, the demonstration of gonococci in the synovial fluid removed by aspiration,

the presence of a positive gonococcal complement-fixation test, and the lack of a response of the arthritis to salicylates. Other diseases of the joints must be taken into account in the differential diagnosis.

DIFFERENTIAL DIAGNOSIS OF GONOCOCCAL ARTHRITIS

In the differential diagnosis, it is necessary to consider other conditions that produce arthritis, and especially those types of arthritis which are likely to be accompanied by conjunctivitis or urethritis. The conditions most likely to be confused with gonococcal arthritis are: (1) acute rheumatic fever, (2) acute pyogenic arthritis (streptococcus, staphylococcus arthritis), (3) postdysenteric arthritis (polyarthritis enterica).

Rheumatic Fever.—Inasmuch as there is absolutely no specific diagnostic test available for the diagnosis of rheumatic fever, it must be recognized by a history, examination, and the clinical course of the disease. From the history, the occurrence of a sore throat, tonsillitis or a respiratory infection preceding the onset of arthritis, one may be suspicious. Within two to three weeks after an infection of the throat or respiratory passages, symptoms of arthritis appear. One should not be misled, however, by the history of a preceding sore throat since Myers and I¹⁵ have observed a number of patients in whom gonococcus infection appeared for the first time after a sore throat. As a rule, however, the arthritis in rheumatic fever appears suddenly; there is pain, tenderness, and at times within twenty-four to forty-eight hours the picture of a hot, red, swollen, tender joint with great pain and limitation of motion is presented. Accompanying the arthritis there is fever varying from 100° to 102° F. or higher. The patient has all the symptoms of an infection and may be extremely uncomfortable. The characteristic feature of the arthritis is its migratory and relapsing character. It generally persists in one joint from one to eight days and may progress from one joint to another. In the simplest variety the disease may be self-limited, lasting about three weeks, but even then low-grade fever, tachycardia, leukocytosis and an accelerated sedimentation rate of the red blood cells may persist, without pains in the joints, indicating the persistence of an active infec-

tion. More often, the disease runs a continuous or intermittent course with relapsing fever, pains in the joints, the appearance of subcutaneous fibroid nodules, erythema, pancarditis, and pleurisy. One of the conspicuous features of rheumatic fever so far as the joints are concerned is the migratory character of the arthritis. This is most unusual in gonococcal infections. The synovial fluid in patients with rheumatic fever has been, in our experience at least, sterile.

Other features which are helpful in establishing the diagnosis of rheumatic fever are: (1) a history of previous attacks of arthritis, tonsillitis or chorea; (2) the presence of cardiac valvular disease with pericarditis and pleurisy; (3) the presence of abnormalities in conduction as determined by electrocardiographic examination.

Acute Pyogenic Arthritis.—Pyogenic infections of the joints usually arise as a result of bacteremia or by direct extension of an infection from the epiphysis into the joint. Usually the diagnosis is not difficult since the signs of suppuration are manifest. Purulent material is readily obtained from the joint and there is often evidence of infection elsewhere. The diagnosis can be made with relative ease by aspiration of the synovial fluid and finding of organisms in the exudate.

Postdysenteric Arthritis (Arthritis Postenterica).—These cases are of importance since they may be accompanied by conjunctivitis and urethritis. During and following an acute bacillary dysentery an acute arthritis may be a feature of the illness. Usually it turns up during convalescence from the symptoms referable to the intestines, commonly appearing between the tenth and the thirtieth days after the onset of illness. The joints most frequently affected are the knees, hips, and hands. With the onset of the arthritis there is fever of indeterminate duration varying from 100° to 102° F., and I have observed it continuing for three weeks. The local condition of the joints is characterized by pain, tenderness, and swelling, limitation of motion, and occasional periarticular swelling with involvement of the tendon sheaths. There is usually no redness of the skin although the surface temperature may be elevated. The fluid is light yellow in color, slightly turbid, and contains moderate amounts of mucin, white blood cells varying between 1000 and 10,000 per cubic millimeter, with polymorpho-

nuclear leukocytes predominating. The fluid is invariably sterile but it may contain agglutinins against the infecting strain of dysentery bacilli. The outlook for complete recovery and normal joint function is excellent in spite of the fact that symptoms may be severe and continue for as long as two or three months.

The diagnosis is based upon a history of an acute bacillary dysentery followed by an arthritis of the larger joints with sterile synovial effusion, and from which complete recovery occurs. When the arthritis is accompanied by a conjunctivitis or iritis or a urethritis, such as was observed in numerous cases by Schittenhelm and Schlecht¹⁶ during the World War, the discrimination between dysenteric and gonorrheal arthritis may be difficult. The bacteriologic examination of the stools, the urethral secretion, together with the history, should make such a differentiation more certain.

Aside from the arthritis following bacillary dysentery, Schittenhelm and Schlecht¹⁶ have described a group of cases under the term of "polyarthritis enterica." These cases are similar in all respects to those following dysentery except for the fact that the lesions in the intestines have not been proved to be due to bacillary dysentery and, indeed, in some patients no intestinal symptoms were known to have preceded the onset of the disorder. It should be remembered, however, that the triad of arthritis, conjunctivitis, and urethritis of a nonspecific character may be present following infection of the intestinal tract and is not due to gonorrhea.

TREATMENT OF GONOCOCCAL ARTHRITIS

The chief objective in treating gonococcal arthritis is to remove the cause, give relief to symptoms, and restore normal function to the joints. The methods of treatment which aim to destroy the organisms are naturally most promising. To accomplish this objective, 3 general methods have been used: (1) specific serum therapy, (2) hyperthermia, and (3) chemotherapy.

Specific serum therapy has not been very successful in the treatment of gonococcal arthritis. In a few cases with bacteremia it has been possible to clear the blood stream of organisms but when the immune serum is injected directly into the

joint cavities, the results have not been at all effective. From our experience it would seem that specific serum therapy should be limited, for the present, at least, to cases of bacteremia.

Hyperthermia is an effective measure in the treatment of a high percentage of cases of acute gonococcal arthritis. Its effect is less striking in cases of chronic and long-standing disease. The main objective of this form of treatment is to increase the body temperature to such a level that the organisms are killed. To carry out this form of treatment effectively it is necessary to use extreme care in the selection and supervision of the patient during the treatment.

Within the last year there has been a revival of chemotherapy in the treatment of gonococcal infection. Sulfanilamide has been used extensively in the treatment of local infections of the genito-urinary tract and, to a less extent, in the treatment of arthritis. Our experience so far with the use of this drug has been limited, but in 2 patients with an infected synovial fluid it was possible to sterilize the fluid within two days after the drug was given, and the organisms could not be obtained from the local lesions in the genito-urinary tract. In patients with sterile synovial fluid, the results seem to be less striking and less conclusive since the course of the disease does not seem to be changed in all of them. This form of treatment deserves a thorough and extensive investigation since there is no doubt that sulfanilamide has a powerful effect on the growth of the gonococcus in various foci of infection.

Inasmuch as gonococcal arthritis is likely to be chronic the patient frequently presents a clinical picture which is so common with any chronic infection: loss of weight, anemia, and atrophy of the muscles about the infected joints. Every effort should be made, therefore, to provide a liberal intake of food, to treat the anemia with iron or blood transfusions, and to care for the patient symptomatically as regards pain and discomfort.

The following procedures should be carried out during the period of convalescence: an effort made to reestablish normal muscle tone about the affected joints through active and passive motion exercises; the arches of the feet given support if the patient has been confined to bed for a long period of time;

and instructions given regarding prophylaxis against venereal disease.

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TREATMENT OF ADVANCED CARDIAC DECOMPENSATION (CONGESTIVE HEART FAILURE)

Diagnosis.—As we all should know, the diagnosis of congestive heart failure depends on evidence of general venous congestion due to failure of the heart to pump blood along as fast as it is fed to it. Familiar as we are with the condition and its symptoms, it is not uncommon to find real confusion between congestive heart failure and (1) many acute and chronic diseases of the lungs, and (2) other diseases that cause local or general edema. It is common (particularly after surgery or confinement) for sudden, alarming symptoms that have nothing to do with the heart to suggest wrongly congestive heart failure. So we cannot be too well informed and practiced in its recognition. A complete description of congestive heart failure would perhaps fill this volume. But in brief, in usual clinical work the following symptoms seem to us the most useful. *Symptoms presumably attributable:* (1) *To congestion in the pulmonary circuit.* There is some degree of orthopnea and of rapid or hard breathing associated usually with diminished respiratory exchange and diminished vital capacity complicated in some cases by variations such as Cheyne-Stokes breathing, expiratory obstruction simulating "asthma," or rounds of apparently unprovoked dyspnea of irregular frequency and duration. There may be cough which may be dry or productive. The sputum may be profuse and blood tinged, or clear blood rarely of large amount. Hoover's sign is usually present. (2) *To congestion in the systemic veins.* If there is no congestive failure, with a patient at rest, supine, and the jugular bulb not below the highest point of the sternum, the neck veins should empty, at any rate after ven-

tricular systole. With a patient in a similar position, in congestive failure the superficial neck veins usually are more or less visible. They may, rarely, be palpable. At present we do not know how to diagnose or gauge congestive heart failure reliably by direct venous pressure estimations. The liver should be swollen and this usually can be detected by careful inspection. Often it is also possible to feel the anterior borders of the swollen liver or portions of it. The liver may be tender and even somewhat painful. (3) *To general aspects of congestive failure.* Cyanosis may or may not be noticeable. It is known that the volume of the circulating blood increases markedly during congestive heart failure. There should, therefore, be a gain in weight from retained fluid. There is also oliguria. There may or may not be demonstrable edema; this should be greatest in the dependent parts.

Now it is, of course, reasonable to attribute the pulmonary congestion to failure of the left side of the heart, and the systemic congestion to failure of the right side of the heart. But one can recognize and treat congestive heart failure and seldom need to consider this differentiation. Except at the onset of acute failure, marked symptoms of failure of the left side of the heart are rarely unaccompanied by some symptoms of failure of the right side. We can construct a clear word picture of rightsided failure due to chronic lung disease that causes embarrassment and finally failure of the right heart. But in practice it is often difficult to be sure that the pulmonary signs are due to chronic lung disease and not, at least in part, to failure of the left heart. And if one finds clear symptoms of rightsided failure unaccompanied by any lung signs, one should at once consider whether the systemic venous congestion is due to some obstruction outside of the heart, such as pericardial disease, mediastinal tumor, or in very rare instances within the heart, to a tricuspid valve stenosis. Dramatic cases could be cited where an intrathoracic goiter caused this symptom complex and where the patient was long treated for congestive heart failure, until finally the correct diagnosis appeared and the goiter was removed surgically with disappearance of the systemic venous congestion.

Though the symptoms of congestive heart failure are of any degree of severity and speed of onset, when they are

clearly recognizable they usually are found in both venous circuits.

From this approach to the treatment of congestive heart failure it would seem that a prime factor in its control would be to increase the output of blood from the heart. Indeed we usually try to do this. We can give digitalis and sometimes other cardiac stimulants in the hope that the output will be increased and the congestion relieved at its source. With a patient in bed, adequate doses of digitalis so commonly are followed by improvement in symptoms of congestive failure that it is seldom that one does not feel that its use is indicated. To be sure, we know that the greatest improvement attributable to the use of digitalis is to be expected where the heart rate is rapid and irregular. Then the control of the disorderly rapid action, in itself a handicap to the heart's ability, is added to the less definite action of the drug in increasing the vigor of the heart's contractions. Only experience with clinical cases has shown us that attempts to stimulate the vigor of the heart's action seldom, if ever, clear symptoms of congestive failure *unless* at the same times the work demanded of the failing heart is markedly reduced. We can scarcely recall an individual seen in congestive heart failure who has cleared the symptoms without going to bed. And we have seen innumerable instances where patients have reported to physicians with symptoms due to congestive heart failure, the diagnosis made correctly, digitalis recommended in adequate doses, but where the patient insisted on continuing up and about and at some semblance of usual activity, without improvement, and then when the patient was finally put to bed, have seen prompt improvement. And we have seen innumerable instances where congestive heart failure has cleared when the patient has been put to bed and given no heart stimulants whatsoever. The main thing, then is to diminish the work demanded of the heart, namely, the volume of blood returned to the heart by the veins.

Another direct method of treating the condition is suggested by the increased blood volume and the very definition of congestive heart failure itself—namely, the removal of a quantity of blood from the congested systemic veins. This has indeed been done and still is done, but as we all know, this

procedure by itself is of limited value and usually not needed if treatment based on removing the load on the heart is thoroughly applied. Where all else fails, or in extremely acute cases, the removal of 8 to 16 ounces of blood promptly through a vein definitely eases the symptoms for a period. In one emergency where violent acute congestive failure complicated by low red blood cell count failed to improve with rest and sedatives and oxygen, bleeding was tried, the blood that was removed was centrifuged and the half containing the corpuscles slowly reinjected, this procedure repeated until 1000 cc. of serum was permanently removed from the circulating blood. The response was gratifying. But such can only be done under most unusual conditions. Indeed, this is almost a unique case in our experience. Rest, with all the familiar aids to rest, is usually so efficacious that we resort to venesection only rarely.

Treatment of congestive heart failure has grown from a study of its contributing causes as shown by the histories of individual patients and by observing the results of attempts to relieve the symptoms at the bedside, rather than from the growing knowledge of the physiologic changes in the circulation, enlightening as this knowledge is.

Putting the Patient at Rest.—With congestive heart failure there is usually breathlessness and orthopnea, muscular tension, and anxiety. In the severest forms the patient endeavors to sit up straight and even strains forward and wishes to stand up. The patient is not at rest until relaxed, the head as well as the body and limbs supported by pillows and not by the patient's effort. (One physician has found that his own basal metabolism estimation varied at the same sitting from a low of minus 15 to a high of plus 25 according to whether he was completely relaxed or lifted his head a fraction of an inch off the table and kept it there during the test.) Undoubtedly some of the severest cases are more at ease with the legs hanging down, as in a chair, than in the usual bed. Though sedatives are usually given, we have found that instructing the patients is even more important. We tell them that their restlessness and breathlessness are a symptom of their condition and that they will only be comfortable when the condition is improved, and that the quickest way to improve the condition

is for them to force themselves to keep utterly still, not even to talk. Where there is marked Cheyne-Stokes respiration, and the patient during the period of dyspnea awakens and becomes muscularly tense and works hard at breathing, the situation is indeed distressing and one wonders if more sedation or stimulation for the respiratory mechanism are needed. On the whole, sedation seems more often to aid. Oxygen by some method is a help. If, then, the patient is still restless and breathing with effort, venesection is suggested. A modification of venesection is the application of tourniquets simultaneously to all four limbs for a few minutes, ten or less for example, and then their removal one by one. The tourniquet should be tight enough to obstruct venous flow but not to shut off arterial pulsation. Sometimes this simple procedure seems to ease the dyspnea for a while. (Occasionally one finds that a patient who cannot be made to breath comfortably by these methods has signs of fluid in one or both sides of the chest. In this situation immediate thoracentesis is indicated. One usually obtains more fluid than one expects and gratifying improvement often follows immediately after its removal. Much more rarely, paracentesis to remove ascites is apparently indicated—never unless the abdomen is tense from the distention. Though cases have been reported where great relief followed incisions in grossly edematous legs in emergencies due to congestive heart failure, situations where this is indicated are rare indeed.) In a sense we should not leave patients in congestive heart failure until comfortably at rest or until we know that they cannot be made so.

Fluid Intake.—Having made the patient comfortable, how can we insure his comfort? Now the patient in congestive failure is waterlogged. Even if edema is not present the volume of the circulating blood is markedly increased. Why, then, do we give such patients any fluids whatsoever by mouth or otherwise? We do not know. Certainly it would seem that the less we can make ourselves content to give them the better. We have occasionally starved patients in congestive heart failure for twenty-four hours. This cannot fail to reduce the amount of fluid they contain. In stubborn cases, where we are trying every way to get them rid of fluid, this simplest of all ways and only certain way (barring direct removal by trochar

or knife) seems to be emphatically indicated. We are so schooled, and rightly so, to fear dehydration in surgical and obstetrical emergencies and in those due to infections—conditions which most of us encounter much more commonly than we encounter severe congestive heart failure, that it seems to us that our judgment is conditioned against the correct control of fluids in congestive heart failure. In cardiac consulting work, it is common to be called to see a patient who has been thoroughly treated with rest, stimulation, diuresis, but who has failed to improve. In many such situations, fluid restriction at the direction of the consultant has improved the apparently stationary condition. We have had patients under our care for years who in the last weeks and months in hospital, under the most favorable conditions, have accumulated fluid in spite of all we did, until they finally reached a stage where *they refused all food and drink*, and while we waited for them to die, have seen their edema lessen with impressive rapidity in a few days. The matter of fluid administration in congestive heart failure is not adequately understood. But we can at least say from our own experience that next to “rest” it seems to us that fluid intake restriction should be our first thought in the treatment of heart failure and in its prevention. Not long ago one still encountered clinicians who said, “You can diagnose heart diseases much better than formerly, but what have you added to the old treatment? What can you do for them except give them rest and digitalis?” Fluid intake control is the first answer. Following are others:

Food control comes next to fluid control in their treatment. Underfeeding is usually safe and indicated. We hesitate to say to just how few calories and for how long one can restrict cardiacs in congestive failure. We know that we have kept patients for days, and even for more than two weeks in rare cases, on the justly famous Karel diet of 28 ounces of milk per day, given in 4 feedings of 7 ounces each, and nothing else. It is seldom necessary to restrict diet so closely for more than two or three days.

In the control of patients, if we had to take our choice between control of their intake and their medication, we would unhesitatingly choose the former. This subject cannot profitably be discussed in brief. We will merely say that a common

diet order sheet for a severely sick cardiac in congestive failure, improving under treatment, would read as follows: "Karell diet." In a few days, "Add 3 tablespoons cooked cereal T. I. D." A few days later, "Diet now: Cooked cereal 3 tablespoons, and milk ounces 8, a.m. and p.m.. At noon. 1 portion meat or fish (remove fat), 1 potato, 1 or 2 tablespoons of a 5 to 10 per cent vegetable. In addition, fruit juice, coffee, tea, water up to ounces 24. Total liquids not more than 40 ounces in 24 hours." Often there are no material additions to this order till the patient is fit to be out of bed.

Diuretics.—Diuretics have been so often discussed that we will merely add our testimony to the general evidence that the modern mercurial diuretics have increased materially the efficiency of the treatment of congestive heart failure. The place for diuretics is naturally after, not before rest and fluid and food restriction.

Direct Removal of Edema Fluid.—As suggested above, removal of fluid from the pleural cavity sometimes is an essential part of emergency treatment. Occasionally it is an aid to the patient who has been put at rest successfully but who has an immense amount of fluid that is slow to clear. It is hard to justify a decision not to remove fluid from the pleural cavity when it is found in a patient in congestive heart failure. We have, however, seen rare cases where fluid appeared in one or the other pleural cavity in patients who were in chronic congestive failure, but where removal of the fluid from the pleural cavity, though adding to comfort for a short time, seemed to lead to more rapid accumulation and the need for its repeated removal. We have wondered in these stubborn cases whether its removal in the long run did good, or harm by allowing further escape of fluid from the blood vessels because of reduced pressure. The same question comes up in chronic congestive heart failure when gross edema elsewhere persists. Shall we tap an ascites? Shall we try removing fluid from the legs by direct incisions, or punctures, or by punctures with Southey tubes? The fluid removed encourages still more fluid to escape and often a lessened output by the kidneys follows. We may be merely making it easy for the edema to reaccumulate. At any rate we have from time to time tried and then abandoned these methods, discouraged by conviction of their

uselessness in a series of cases and by the real discomfort they caused from soaked bedding and by an occasional sepsis starting at the point of incision or puncture.

Purging may be tried, but it is tiring and may result in distress from irritated bowels. If enemata are given we must remember that we may be adding materially to the patient's fluid intake by water absorbed by the bowel.

Pressure by massage and bandaging has been tried but is rarely indicated. Sweating and applications of some preparation to the skin designed to remove edema fluid by osmosis have been tried. So have leeches. These methods nowadays do not seem to offer much aid. Should we try a salt-free or modified salt-free diet? Or should we give salt in large amounts? Some believe deliberate salt control is more or less useful. The treatment of dropsy is an old problem. Many physicians have puzzled over it and we are always learning more about it.

When Shall We Begin to Increase the Patient's Activity?—The first principle is to continue efforts along the lines suggested above until "all signs of congestive failure have cleared." Breathlessness, orthopnea, moisture in the lungs, edema, full neck veins and swollen liver all may disappear, and still if we watch the patient carefully we may find that beyond this point improvement in the movements of the chest with deep breathing, in vital capacity, and continued loss of weight indicating further removal of concealed fluid, continues. There is another factor in deciding when we shall begin to let the patient out of bed and see how much he or she can do. It seems evident that a patient who has just lost all signs of congestive failure is not in such good condition as a similar patient, still under conditions which allowed the improvement, who lost them three weeks ago. We have long made it a rule to keep patients in bed for three weeks after all signs of congestive failure have cleared. We cannot measure the "fatigue" of their heart and of their body in general which we hope will have been lessened by these three weeks of rest. We do know that we have seen patients get out of bed under careful restrictions directly after the loss of their signs of failure and promptly have some of the signs of failure return, and have then repeated the careful treatment, adding three weeks

of rest, and the signs of failure have not returned after letting them up on the same plan. The three weeks' rule is mostly arbitrary. There is slight support for it in that intra-cardiac thrombi, which form more easily during severe congestive failure, are said to need at least three weeks to become at all firmly adherent to the heart wall. It may be that we avoid some embolisms by keeping our patients at rest for three weeks after all signs of failure have cleared before letting them up.

Removable Burden.—In the background of the patient in congestive heart failure, careful questioning and thought detects many indications for its treatment and prevention. (1) Sudden changes in the heart itself: The onset of disorderly, or rapid, or very slow rate, or active rheumatic disease, or a coronary occlusion. And (2) outside the heart, the factors which may be considered as indirect "burdens" on the heart that directly provoke its failure, such as an infection anywhere, pregnancy, hypertension, hyperthyroidism, anemia, overeating, overdrinking, overexertion, fatigue. These and many other factors should come to our minds when we are treating a patient in congestive heart failure. The general principle of *searching for and removing removable burdens* on the heart is illustrated by the following case histories.

Case I.—A housewife, aged forty-one, when first seen was apathetic, emaciated, edematous. Her heart was slightly enlarged and the pulse rate rapid and irregular. There was dyspnea and moisture at the lung bases. The liver was enlarged. Its borders 2 or more inches below the costal margin. There was moderate edema of the dependent parts. The thyroid gland was symmetrical and easily palpable and the eyes slightly prominent. The palpebral fissure was widened, giving a staring appearance. She had become thinner and more disabled by breathlessness for one and one-half years till her present bedridden state of complete disability from congestive heart failure. She failed to respond to treatment directed at the heart. Subtotal thyroidectomy was followed by disappearance of all signs of congestive failure within two weeks, and she has led a normal life without return of failure for years.

Case II.—A salesman, aged forty-three, a heavy beer drinker, noted edema following a month of extra heavy drinking. There was breathlessness, cough, orthopnea. He was put to bed and given a modified Karell diet and digitalis, with little or no improvement. One week later, seen in consultation, he showed, in addition to the above signs, râles at the lung bases, full neck veins, a large liver, a heart moderately enlarged with forceful action. There were gallop sounds but no significant murmurs. The heart beat was rapid and regular. The blood pressure was 150/70. The electrocardiogram showed changes that were attributable to digitalis. The urinalysis and blood chemistry were negative. Large doses of brewer's yeast added to the modified Karell diet were followed by marked improvement within three weeks. Following a period of thirty-six hours when the patient suddenly left home without leave and devoted his time to drinking beer there was a return of symptoms. Convinced by this he went to bed and followed treatment carefully. He recovered and has continued to lead a normal, active life for two years on a diet without alcohol. He has had no symptoms.

Case III.—A housewife, aged forty, for six years had had profuse, irregular bleeding from the uterus. She had avoided surgical and medical treatment and had relied on the spoken and written word. She became breathless and dropsical and finally gave up and entered a hospital. She had all the signs of congestive heart failure. There was moderate hypertension and profound secondary anemia. The usual treatment for congestive failure, with iron and liver for her anemia, improved her condition so that she was operated successfully. She has led a normal life without symptoms for five years.

Case IV.—A nurse, aged thirty, had rheumatic fever in childhood. Her heart showed a systolic murmur and a doubtful enlargement. She had led an active life until a few weeks before admission to the hospital when she caught the "grippe." She continued to have a fever, dyspnea, and beginning edema until forced to come to the hospital. At entrance she showed severe congestive heart failure, fever, a blood pressure of 140/60, and a hemoglobin of 35 per cent, with a red blood

count of 1,800,000. The patient was in extreme condition. When she failed to improve with morphine, rest, oxygen and digitalis, it was hoped that a blood transfusion to improve her anemia might help her. Two hundred fifty cc. were given slowly when she suddenly became extremely dyspneic and died. Autopsy showed subacute bacterial endocarditis and chronic mitral disease.

Case V.—A housewife, aged sixty, previously well, had a coronary occlusion. Two days later her pulse and ventricular rate suddenly fell to 28. An electrocardiogram showed complete heart block. Signs of severe congestive failure appeared at once. Ephedrine sulfate injected subcutaneously was followed in a few moments by a rise of her heart rate to 90 and a resumption of normal rhythm. The signs of congestive failure cleared. The ephedrine sulfate was continued, normal rhythm was maintained, and the patient recovered.

Case VI.—A housewife, aged forty-three, was first seen at twenty-one years of age when eight months pregnant and in severe congestive failure. At this time she had a slightly enlarged heart and a mitral diastolic murmur. She was successfully delivered. One year later she became pregnant again. Congestive heart failure reappeared at the third month. The pregnancy was interrupted. Her child is now twenty-two years old. Her weight now is the same as at the time of her marriage. Her heart shows mitral stenosis and a moderate enlargement. Her teeth and blood are in excellent condition. She has continued an a régime with carefully measured physical expenditure but free enough to enable her to lead an effective life as housewife and mother. She has had no return of congestive failure.

Case VII.—A housewife, aged twenty-five, with a moderately enlarged heart with mitral stenosis entered a hospital in severe congestive failure, four months pregnant. Her failure improved at first, then became more and more severe until at the end of the eighth month she was delivered by hysterotomy. She died three days later. Her first 4 pregnancies had been successful though she had slight congestive failure in the

fourth. In the fifth pregnancy she failed and miscarried at the sixth month. During the six years of her married life she had become obese. She had oral sepsis to a severe degree. She worked each day to the limit of her strength.

Case IV suggests much. It shows the danger of injecting fluid, even slowly, into the veins in congestive heart failure. It also suggests that in severe congestive failure, whatever the cause, one should first treat the failure, then remove its cause.

Case I, however, shows that sometimes the first step may never be completed until the second one is taken. Fortunately or unfortunately there are few hard and fast rules to guide us.

It is, however, hard to divorce the treatment of congestive heart failure from its prevention. Time and again its successful treatment means the application of principles that might have been used to prevent it.

We should make it a hard and fast rule to search for and vigorously remove removable burdens as soon and thoroughly as our individual judgment allows. The most common ones are not dramatic as in some of the cases quoted, but humdrum things like weight reduction. In our hospital wards we often find women, and sometimes men, of sixty years or thereabout in congestive failure that apparently is merely the result of the degenerative changes of age. But if we question them, we find that they now weigh 50 or more pounds over their weight at say twenty-five years of age. They seem to be weighted to their beds, not by age but by fat. "One cannot get a cardiac too thin" is a therapeutic catch phrase that appeals to us in the light of our experience.

Even the principle of removing burdens from the heart may lead us in strange directions if we follow it too hard and fast. If we confine the principle to the removal of *undesirable* burdens we have our cardiacs slender, with normal blood counts, free from oral sepsis, protected by régimes against fatigue, overexertion, warned to make allowances for intercurrent infections, warned to report for regular examinations so that disorders of the heart beat, tumors, hyperthyroidism, malnutrition, and many other treatable or preventable burdens may be anticipated or recognized early. They are getting the most out of life in spite of their damaged hearts.

Other methods of removing burdens which are not in them-

selves undesirable but are indeed desirable are offered from time to time: Removal of the spleen to reduce the amount of venous blood seeking a return to the heart through the liver; and recently the removal of a normal thyroid gland. It will no doubt be possible to add to this list. One can visualize theoretical cases, if these procedures were multiplied, granting the immediate safety of the treatment, where the price paid for the improvement was clearly great. This point of view is offered for consideration and not to imply that no such methods of treatment are ever justified. We rarely see at present a situation where they seem clearly indicated in our opinion. We wish to say, however, that in our opinion thyroidectomy for congestive heart failure with no hyperthyroidism, whatever its other value, has made one definite contribution to treatment. It has indirectly shown again the fact that subtotal thyroidectomy in disabled cardiacs is comparatively safe. We occasionally see disabled cardiacs who suggest a possible underlying hyperthyroidism. Sometimes we cannot make up our minds definitely that the hyperthyroidism is there. Subtotal thyroidectomy is indeed a very safe operation. It is rarely followed by myxedema or tetany or other unpleasant sequelae. It usually cures hyperthyroidism promptly. Furthermore, if a cardiac in heart failure has an underlying hyperthyroidism, the heart failure usually persists in spite of all other treatment till subtotal thyroidectomy, and then is cured for good. Such cases are rare, and we should search for them. They offer extraordinary opportunity for gratifying results. We should not be too cautious in offering subtotal thyroidectomy to those rare patients in congestive heart failure in whom we strongly suspect an underlying hyperthyroidism.

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SYMPOSIUM ON MEDICAL EMERGENCIES

The following clinics are included in this Symposium:

Edwin G. Bannick: INTRODUCTION.

George B. Eusterman: MEDICAL ASPECTS OF GASTRO-INTESTINAL EMERGENCIES.

Fredrick A. Willius: SOME CARDIAC EMERGENCIES.

Byron E. Hall, Malcolm M. Hargraves, Charles H. Watkins and Herbert Z. Giffin: EMERGENCIES ARISING IN THE ANEMIAS AND BLOOD DYSCRASIAS.

Edgar A. Hines, Jr.: THE DIAGNOSIS AND TREATMENT OF EXTRACARDIAC VASCULAR EMERGENCIES.

Melvin W. Binger: RENAL EMERGENCIES.

Hugh R. Butt: COMMON EMERGENCIES ARISING IN THE COURSE OF HEPATIC DISEASE.

Edwin J. Kepler: DIAGNOSIS AND TREATMENT OF EMERGENCIES ASSOCIATED WITH DISEASES OF SOME OF THE DUCTLESS GLANDS.

Earl C. Elkins: COMMON EMERGENCIES RESULTING FROM CONTACT WITH CERTAIN PHYSICAL AGENTS.

INTRODUCTION

EDWIN G. BANNICK

IN the present era of specialization in medicine, accurate diagnosis and rational treatment of disease have been developed to a high degree. As a result of clinical, physiologic and chemical research, measures are now available for the diagnosis and treatment of certain diseases, the nature of which has heretofore been somewhat obscure and the treatment of which has been unsatisfactory. Such measures, however, frequently require the aid of a well equipped laboratory, and there has perhaps been a tendency on the part of physicians to depend more on these laboratory aids and less on their clinical judgment. In certain difficult and complicated cases, this tendency may be justifiable, and even though laboratory examinations may require considerable time, they may be essential to the correct diagnosis and management of the case.

The proper handling of other cases, however, depends chiefly on broad knowledge, clinical experience, and excellent judgment on the part of the physician and frequently demands prompt and decisive action. In this latter group are the various surgical and medical emergencies. The physician who is first called on to meet such emergencies employs his broad general knowledge of medicine and of its various special fields. His clinical judgment will enable him to decide quickly when emergency treatment is indicated. If he can be reasonably certain of the correct diagnosis he will know the proper treatment, and if his facilities do not permit him to administer such treatment adequately he consults with someone who is qualified to do so. If he cannot be certain of the correct diagnosis, he at least appreciates the possible causes of the trouble, the treatment that would be indicated, and the complications that might arise from each cause, and then carefully plans his treatment accordingly. In the absence of a positive diagnosis,

the highest degree of clinical judgment is necessary. Delay and uncertainty at such a time may lead to serious mistakes. Above all, the best physician recognizes the limitations of his medical knowledge and skill and is honest with himself and his patient.

Nowhere in the field of medicine are the honesty and integrity of the physician of more value than in these emergency cases, and nowhere is the relationship between patient and physician closer. The patient must have complete confidence in his physician who in turn must not betray this trust either through selfishness or through lack of knowledge. It is no easy matter for physicians to maintain the store of information which is necessary under these circumstances, and the medical profession as a whole should endeavor in every way possible to make this task easier.

The following Clinics are, therefore, devoted to the discussion of some of the common medical emergencies and it is hoped that they will be of some value in summarizing the present status of the diagnosis and treatment of these conditions.

MEDICAL ASPECTS OF GASTRO-INTESTINAL EMERGENCIES

GEORGE B. EUSTERMAN

THE purely medical aspects of abdominal emergencies are, chiefly, those of diagnosis, preparation of the patient for operation, and treatment of conditions the presence of which defer or contraindicate operation. The physician is, usually, the first to contact the patient and, therefore, upon the physician is placed the grave responsibility of as prompt and accurate an appraisal of the situation as circumstances permit and of securing, without delay, surgical consultation when indicated, or whenever any reasonable doubt exists. The physician must be as mindful as the surgeon of the rapidity with which disastrous changes can occur in the abdomen and of the factor of delay, or indecision which allows, too frequently, an acute abdominal emergency to become an abdominal disaster. On the one hand, the physician, more cognizant than the surgeon of the extra-abdominal origin of many urgent gastro-intestinal symptoms and signs, may be guilty of procrastination or ultra-conservatism; on the other hand, the surgeon may be too rash and may realize after opening the abdomen, that the trouble is elsewhere. This results in embarrassment to the surgeon and in needless suffering and risk for the patient.

GENERAL DIAGNOSTIC CONSIDERATIONS

Symptoms usually characteristic of a gastro-intestinal emergency are severe abdominal pain, vomiting, and hemorrhage, or a variable combination of these symptoms. Prostration, shock, and even delirium and coma may coexist or supervene. The diagnostic significance of these symptoms and the more frequent conditions or complications underlying them will be discussed briefly, seriatim. When severe pain domi-

nates the picture, especially in association with such noteworthy signs and symptoms as localized tenderness, muscular rigidity, distention, nausea and vomiting, surgical possibilities should be the immediate concern of the medical attendant. But, in order that the abdominal symptoms and signs are not like a "red herring drawn across the trail to confuse the examiner and conceal the true condition" as Lick aptly expressed it, certain procedures compatible even with an emergency should be carried out, namely: (1) appraising of the evidence deduced from the immediate history, complete physical examination, temperature, pulse rate, blood pressure, and from microscopic examination of the blood and urinalysis when available; (2) obtaining details of habits, previous illness, and symptoms antecedent to the present acute illness; (3) carrying out with dispatch certain biochemical, serologic, electrocardiographic, or roentgenologic examinations in the presence of atypical or complicated conditions. Fortunately, the first two procedures supply the necessary information for adequate diagnosis of the majority of abdominal emergencies.

PAIN

We have alluded already to the significance of pain and certain associated symptoms and signs characteristic of the majority of acute abdominal lesions or complications such as perforation, obstruction, intussusception, infarction, torsion, volvulus, abscess and so forth which usually require direct surgical interference. The nature of such lesions and their diagnostic and surgical aspects recently have been summarized in an instructive article by Abell. With such lesions, exclusive of their diagnostic aspects and symptomatic and supportive treatment, we as physicians, are not so directly concerned here. Possibly, exception may be taken in two instances: (1) that form of subacute (protected, *forme fruste*) type of perforated peptic ulcer which, at the outset, closely simulates acute perforation, in nature, if not in degree, but from which the patient usually recovers without surgical interference, and (2) those instances of acute gastritis or gastro-enteritis which also, respectively, may simulate acute perforation of an ulcer and acute appendicitis, as was emphasized recently by Kloss-termeier and by Dietrich.

The extra-abdominal causes of severe abdominal pain are numerous and no one is more aware of that fact than the experienced internist who has perspective and a background of broad training. Careful anamnesis and systematic physical examination are the first safeguards against erroneous interpretation. Age and sex of the patient often play an important rôle in differential diagnosis. Among children, nonsurgical causes of abdominal pain may be ordinary colic, mesenteric lymphadenitis, pneumonia, acute pyelitis, acute enterocolitis, abdominal tuberculosis, threadworm, Henoch's purpura, and so forth. Organic lesions of the digestive tract proper are, at least, four times as frequent among men as among women, but disorders of a psychoneurotic or an hysterical nature and cholecystic disease greatly predominate in the female. In the reproductive period, acute abdominal pain may be the result of ruptured ectopic pregnancy, acute pelvic peritonitis, and rupture or torsion of an ovarian cyst.

Abdominal pain and increased tension of the upper portion of the rectus and oblique muscles, occasionally associated with lobar pneumonia or with pneumonia that involves a lower lobe and is associated with diaphragmatic pleurisy, may be mistaken for acute appendicitis, especially among children; such conditions among adults may excite suspicion of leaking duodenal ulcer or acute cholecystitis. Mistakes can be avoided by patient and thorough physical examination. When inflammatory lesions are above the diaphragm, in contrast with those below it, the respiratory rate is quickened, there is an early increase in temperature to as high as 102° F. (38.9° C.) or higher, and movement of the alae of the nose is perceptible. The abdominal rigidity is more like a stiffness in contrast with the extreme boardlike hardness associated with perforation. The lower portion of the abdominal musculature is more relaxed, as a rule, than it is in the presence of peritoneal involvement. Careful examination of the thorax with a stethoscope may reveal, at the very outset of the attack or soon thereafter, fine, crepitant râles at the bases, a friction rub, or an area of bronchial breathing.

Surpassing in frequency and importance the inflammatory lesions within the thorax, are diseases of the circulatory system, coronary disease in particular. The occasional epigastric

situation or reference of the severe pain of paroxysmal angina pectoris, and the severe oppression or agonizing pain of sudden coronary occlusion is often difficult to distinguish from the pain of perforated ulcer, biliary colic, acute pancreatitis, or mesenteric infarction. It is recalled that an epigastric situation of pain, nausea, vomiting, fever, and leukocytosis may be common to both coronary occlusion and the aforesaid acute abdominal conditions.

Helpful in differentiation of these conditions are the following features: 1. On the one hand, there is usually an antecedent history of angina pectoris, hypertension, syphilitic infection or positive Wassermann reaction (syphilitic aortitis), and other cardiac symptoms or signs and, on the other hand, there is a history of former attacks of indigestion, hemorrhage, colic, or jaundice. Other signs and symptoms indicative of the thoracic origin of the attacks are poor heart sounds, usually a low blood pressure and weak pulse, eventually a pericardial friction rub and significant electrocardiographic abnormalities, such as changes in the T wave, intraventricular or auriculoventricular block. 2. The large majority of the victims of coronary accidents are middle-aged or elderly men, whereas acute abdominal emergencies are common to both sexes in that period of life; however, acute perforating ulcers occur much more frequently among men than among women. 3. Although the pain of coronary occlusion appears to be solely epigastric in situation, usually it is also substernal and often is projected into the arms, especially the left. 4. Examination of the abdomen may give evidence of an inflammatory or a neoplastic mass, a consistent localization of tenderness and muscular rigidity, aggravation of the pain by movement of the patient, the presence of jaundice, or bleeding of a gastroenteric nature.

Sometimes the coexistence of a lesion in the thorax and in the abdomen adds to the diagnostic perplexities. Willius has pointed out, for example, the frequent coexistence of coronary disease with disease of the biliary tract, both of which contribute to the symptoms and signs present. Other less frequent thoracic causes of severe abdominal pain are rupture of an aneurysm of the thoracic aorta, acute pericarditis, and spontaneous pneumothorax.

On the other hand, the pain engendered by intra-abdominal lesions may be referred exclusively to the thoracic region. Disease and dysfunction of the cardia and lower portion of the esophagus, para-esophageal hernia, gastric and duodenal ulcer, and calculous cholecystitis occasionally may mimic the anginal pain of coronary insufficiency by virtue of such transposition or extension. The severe, sustained pain of a penetrating ulcer or gallstone rupturing into an adjoining viscus, the rare strangulation, torsion or volvulus of an inverted portion of thoracic stomach complicating diaphragmatic hernia, may give rise to an erroneous diagnosis of angina pectoris or acute coronary occlusion. In White's experience, nausea and vomiting exclusive of sudden coronary occlusion, always favor the diagnosis of trouble below the diaphragm unless induced by morphine given for the relief of pain or by excessive amounts of digitalis given for relief of real or fancied myocardial failure. Hiccup and jaundice, likewise, have the same diagnostic significance. Obviously, the electrocardiogram is invaluable in detection of disease processes above the diaphragm, just as use of a barium meal in roentgenologic studies, and cholecystography are indispensable to detection of intra-abdominal disease. Aynesworth stressed the importance of making immediate decisions regarding acute intra-abdominal surgical lesions but minimized the risk of delay in making a diagnosis if the disease is above the diaphragm.

There remain a wide variety of extra-abdominal or nonsurgical causes giving rise to acute abdominal pain. The importance of prompt, routine, chemical, and microscopic examination of the urine is attested to by the fact that lesions of the upper portion of the urinary tract, and diabetic acidosis, for example, may engender severe pain and other alarming disturbances of a gastro-intestinal nature. The visceral crises of tabes dorsalis, especially the painful gastric type, always must be borne in mind as well as the possibility of abdominal migraine, periarteritis nodosa, allergic states, and poisoning owing to lead and arsenic. Here again the nature of antecedent illness, occupation, and systematic physical examination may furnish the first clue as to the source or nature of the trouble. Even disorders of such remote organs as the thyroid cannot be excluded. Robertson and his associates recently reported two

cases of hyperthyroidism that simulated appendicitis closely, the symptoms disappearing after administration of compound solution of iodine. Protracted vomiting or diarrhea during a thyroid crisis also may necessitate adoption of prompt emergency measures.

VOMITING

Vomiting of such severity or duration sufficient to assume emergency proportions is by no means infrequent even if we exclude such entities as cyclic vomiting of children and hyperemesis gravidarum, conditions which do not come within the scope of this contribution. Paradoxical as it may seem, severe seizures of vomiting, in my experience, have their origin more frequently in conditions outside the digestive tract proper than within it. The causes of such crises may be psychogenic, neurogenic, toxic, organic, or mechanical. Outstanding examples of these are nervous or hysterical vomiting which usually affects women, tabetic gastric crisis, severe seizures of vomiting which may occur among patients who have migraine, brain tumor and labyrinthine disease. Those of toxic origin are associated with such conditions as alkalosis or acidosis, whether the cause be acute alcoholism, uremia, acute hyperthyroidism, or acute adrenal insufficiency. Organic intra-abdominal conditions are acute phases of appendiceal, cholecystic, and pancreatic disease, obstructing, inflammatory, cicatricial, and neoplastic lesions of the stomach, duodenum, and upper intestinal tract.

Although we may be interested primarily in the retention types of vomiting of pyloric obstruction, it must be remembered that vomiting may be absent in spite of this complication. We must be mindful, also, of a type of nonobstructing duodenal ulcer (*ulcus à forme tabétique*), the symptoms of which may be characterized exclusively by recurrent attacks of persistent and protracted vomiting, closely simulating, in this respect, the gastric crises of tabes. Emergency states characterized by severe vomiting and toxemia, erroneously attributed to pyloric obstruction, are often the result of excessive doses of alkali taken during treatment for otherwise uncomplicated ulcer. Ulcer-bearing patients who have associated hepatic, renal, or arterial disease with hypertension particularly are liable to this form of intoxication.

Equal in importance to ascertaining the cause and controlling the vomiting, is correction of the toxemia which so frequently follows. Failing to recognize and to combat the seriousness of this toxemia were two of the greatest factors in the high surgical mortality among patients suffering from pyloric or intestinal obstruction who were submitted to operation. All this has been changed in the last fifteen years, thanks to proper preoperative preparation. Such toxemia is characterized by increased nonprotein nitrogen of the blood, alkalemia or acidosis, hypochloremia, and dehydration. Severe diarrhea from whatever cause, as well as vomiting, which materially upsets the fluid and inorganic salt balance and acid-base equilibrium of the blood, will bring about this dangerous state. Adequate parenteral administration of fluid and restoration of the salt balance soon restores the patient to a normal condition.

HEMORRHAGE

Massive hematemesis or melena, or both, having their origin in gastroduodenal ulceration is the cause of death of 13 to 30 per cent of patients admitted to large charity hospitals because of such hemorrhage. In general practice, the mortality rate is estimated to range from 1 to 3 per cent. Death during or following the first hemorrhage of severe proportions ranges from 9 to 15 per cent. Duodenal ulcer is the commonest source of hemorrhage, although the tendency to bleed is associated more markedly with gastric ulcer which, however, is encountered clinically much less frequently. Other intrinsic sources of hemorrhage are anastomotic ulcer, gastric carcinoma, benign gastric tumor, and gastritis, especially the chronic hypertrophic form associated with erosion or ulceration. The more frequent extraneous causes are portal cirrhosis and splenic anemia. The latter conditions give rise to varices in the lower esophagus and stomach. In about 25 per cent of such cases, there is a history of recurrent hemorrhage and, in 50 per cent of the patients who have bled, hemorrhage may recur after operative interference.

Authorities generally are agreed that age is the greatest factor affecting prognosis. Necropsy findings in the majority of the fatal cases revealed erosion of a sclerosed vessel in the base of a chronic penetrating, or perforated, indurated ulcer

on the posterior wall. In spite of some opinions to the contrary, usually it is difficult to determine which patients with massive hemorrhage will survive and which will not. In my judgment, the middle-aged or elderly patient suffering from a chronic lesion should be submitted to operation without delay if he has bled on previous occasions, if he does not respond favorably to treatment as indicated by blood pressure, pulse rate, value for hemoglobin, erythrocyte count and level of blood urea (all estimated at stated intervals) and if, in addition, he shows signs of shock, or hemorrhage appearing and then recurring within a short interval.

In recent years, a number of observers have pointed out that massive intra-intestinal hemorrhage gives rise to certain derangement in the functions of the organism characterized chiefly by marked elevation of the blood urea (extrarenal uremia), a decrease or cessation of excretion of sodium chloride in the urine, urobilinuria, and a decrease of the content of albumin of the blood. Increase in blood urea is the most constant symptom, appearing within a few hours following the hemorrhage and persisting for a shorter or longer period. In spite of the acholuria, the blood chlorides may be normal or even increased. The mechanism underlying this phenomenon is still a matter of dispute. When the greater part of the blood is vomited and little reaches the intestinal tract, these biochemical changes do not occur; thus, presence of blood in the intestinal canal is an essential prerequisite for development of the increased concentration of blood urea. Christiansen is convinced that these changes, when present, have definite prognostic and therapeutic implications.

TREATMENT

When the nature of an acute abdominal seizure has not been determined, it is the universal custom to withhold opiates until reaching the decision that operation is contraindicated or is to be temporarily postponed. Guerry's statement that "morphine puts two people to sleep, the patient on the one hand and the doctor on the other" tersely expresses the reason for such custom.

By and large, this is probably the safest procedure to follow if suffering and shock are not too great. On the other

hand, such a competent and an experienced internist as the late Harry Singer, on the basis of observations made by Hildebrandt and Zierold, advocated the *intravenous* use of $\frac{1}{4}$ grain (0.016 gm.) morphine sulfate or $\frac{1}{20}$ grain (0.003 gm.) of dilaudid, if, on account of the severity of the pain, it is difficult or impossible to secure the patient's coöperation in obtaining a satisfactory history or making a proper physical examination. However, before morphine or dilaudid is given, a sketchy anamnesis is obtained, a preliminary physical examination is made, and the observations are *recorded*. On administration of morphine or dilaudid in such a manner, relief is prompt, the abdomen is relaxed, and the hyperesthesia is more or less eliminated. With a fair degree of accuracy the examiner can then determine: (1) the location of the point of maximal tenderness, (2) the degree of tenderness, and (3) the presence or absence of any abdominal mass. Observations made before and after morphine has been administered then can be reviewed. Suffering, exhaustion, and shock are greatly reduced and this renders the patient a better operative risk.

This method has much to commend it and, although it has certain disadvantages, they are by no means insurmountable. When the patient is relieved he may decline or delay laparotomy. Therefore the patient or his relatives must be informed of the selective action of the opiates on the pain and of its failure to influence the course of the disease. Also, in the presence of a mechanical obstruction, the very active peristalsis heard synchronously with the height of the paroxysmal pain may disappear. But, by reverting to data recorded *prior* to administration of the opiate, the physician will *not be deprived* of any useful data, in the opinion of those *who advise* that morphine should be given intravenously early in the period during which diagnosis is being attempted.

When acute pain is due to nonsurgical conditions, the rational treatment is, obviously, that of the *underlying cause* as soon as it is determined. If the pain is *excessive* for any reason, morphine or its equivalents may be *resorted to* promptly with few misgivings. Use of vasodilators or antispasmodics not only may relieve the patient but *also* may distinguish the pain of angina pectoris or the *painful visceral* species of *fluor*

tional origin from pain of acute inflammatory visceral disease or its complications.

In treatment of vomiting of emergency proportions, it is essential, of course, to determine whether or not mechanical obstruction is present and, if so, to determine the level of the obstruction as well as the degree of toxemia present. Obstruction at or just below the pylorus usually requires preliminary gastric lavage, restriction of food to a semisolid or liquid type, and intravenous administration of a solution of 1 per cent sodium chloride, preferably with a solution of 5 to 10 per cent d-glucose. This is especially important if there is an elevation of the nonprotein nitrogen of the blood, hypochloremia, and an increased combining power of the blood for carbon dioxide. Obstruction, the result of benign inflammatory lesions at or just beyond the pylorus, frequently is overcome after a few days of treatment, sometimes permanently. Obstruction of a cicatricial or malignant nature requires surgical interference as soon as dehydration and toxemia have been corrected, assuming the condition is operable.

Vomiting owing to high intestinal obstruction is profuse and recurrent and, within forty-eight hours, is attended by profound toxic changes such as have been described. Intravenous treatment is urgently indicated and is administered similarly to that for pyloric obstruction. In addition, transfusion is usually necessary in all strangulating forms of obstruction; use of suction also is necessary. The latter is accomplished by introduction of a Levine tube through the nose into the stomach; the end distal to the patient is attached to a simple water siphon. Simple obstruction, especially that owing to adhesions, often may be managed satisfactorily, without resorting to operation, by the method of conservative decompression as advocated by Wangensteen.

Functional or nervous vomiting, a common disorder chiefly afflicting women, as previously noted, often responds favorably to proper treatment. The procedure usually carried out at the Clinic has been described by Drenckhahn and Wilbur. Severe toxemia as profound as that encountered among patients who have complete pyloric obstruction may occur.

Nondiabetic acidosis may be caused by loss of alkaline secretions such as occurs in the fluid stools of persons who

have severe diarrhea, or owing to fistulas of the small intestine and bile ducts. In about half of the cases of ileal obstruction and in the majority of those of colonic obstruction, this type of toxemia is observed. Therefore, in order to distinguish alkalosis from this form of acidosis, determination of the carbon dioxide combining power of the plasma is essential for the reason that intravenous injection of an isotonic (1.3 per cent) solution of sodium bicarbonate is indicated in treatment of acidosis instead of saline solution which is given for correction of an alkalosis. To prevent overdosage with the alkaline solution, Kirk urged the use of the nomogram of Palmer and van Slyke.

Treatment of profuse hemorrhage from the stomach or duodenum is chiefly of a medical nature because of the fact that operation in the course of, or soon after, hemorrhage, is avoided by the surgeons because such a procedure is attended by a higher mortality rate than medical treatment. The best method of treatment is still a matter of dispute. On the one hand are those who advocate such active measures as lavage of the stomach to remove clots, followed by continuous suction and immediate feedings, while on the other hand are those who even hesitate to give a transfusion for fear of dislodging a thrombus or elevating the blood pressure and thereby cause a recurrence of bleeding. The expectant method is still the one most in vogue, namely, complete rest, opiates, partially filled ice bag applied to the abdomen, the usual measures directed toward treatment of shock if present, transfusion of blood when indicated, and withholding food for several days. There seems to be no effective local or systemic hemostatic or thromboplastic, such as bile and vitamin K promise to be for hemorrhages associated with severe jaundice. Continuous transfusion of blood, such as advocated by Marriott of London, the Meulengracht dietary regimen, the continuous administration of aluminum hydroxide solution by the drip method, fluids or foods containing large amounts of vitamin C, reinforced by synthetic vitamin whenever indicated, and the use of snake venom for capillary bleeding, constitute recent advances in the treatment of this emergency. Under certain circumstances, as previously noted, early recourse to operation may be indicated.

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SOME CARDIAC EMERGENCIES

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CORONARY THROMBOSIS

THE most frequently encountered cardiac emergency is coronary thrombosis. This disease has received so much attention during recent years that one hesitates to enlarge further the already tremendous literature on the subject. Nevertheless, coronary thrombosis is of great importance owing to its constantly increasing occurrence, its more frequent appearance in atypical form, its increasing incidence in the younger age groups, and because it is so commonly overlooked, and frequently, when recognized, is so poorly treated. These facts alone may justify reëmphasis of certain phases of the diagnosis and treatment of this disease.

Most physicians now experience little difficulty in identifying coronary thrombosis when it appears in its classical form. This well-known syndrome comprises severe retrosternal or epigastric pain or distress, usually enduring for an hour or longer, occurring with or without regional distribution. The pain may be continuous for several hours or may be recurrent with variable periods of abatement. Phenomena of shock, such as cold perspiration, pallor, abrupt fall in arterial blood pressure and weak, rapid pulse frequently supervene soon after the onset of the pain. Fever, ranging from 99.5° F. to 101° and 102° F., appears within twelve or twenty-four hours, moderate leukocytosis occurs and, at times, a pericardial friction rub is audible over the precordial area in the first, second or third day. The sedimentation rate frequently is accelerated.

It is not unusual, however, for the subjective phenomena to appear without the striking and dramatic evidences of shock. The absence of signs of shock should never militate against the diagnosis of coronary thrombosis.

From time to time coronary thrombosis manifests itself without pain. The sudden onset of severe dyspnea, frequently with ensuing edema or marked congestion of the lungs, heralds this condition. Again, phenomena of shock may or may not be present. This syndrome, so frequently called "cardiac asthma," is dependent on sudden failure of the left ventricle. Therefore, while coronary thrombosis is capable of producing this clinical picture, obviously other cardiopathies are likewise able to produce this syndrome. The electrocardiogram is always helpful in making differential diagnosis.

Less frequently, coronary thrombosis occurs without pain or marked dyspnea; the outstanding symptoms are the sudden onset of weakness, profuse perspiration, and other mild phenomena of shock.

In other instances, the primary evidence of the episode of occlusion may be distinguished with difficulty from the ordinary anginal seizure. The duration of pain may be relatively brief; perhaps it will last only ten or fifteen minutes but will tend to recur within the first twenty-four hours. Other symptoms and signs may be entirely absent. The presence of coronary thrombosis always must be presumed, until its absence has been proved, in the event of a first anginal attack and if the seizures are frequently recurrent.

The first consideration in the management of these situations is the prompt recognition of the condition. If uncertainty regarding the correctness of the diagnosis exists, one should institute treatment as though no doubt existed regarding the presence of coronary thrombosis. The patient promptly should be placed at complete rest in bed and should not be permitted to be ambulatory even for a brief period. When pain is severe or tends to persist, morphine sulphate in doses of $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016 to 0.032 gm.) is administered subcutaneously and the administration is repeated within a reasonable time if relief is not definite.

From there on, the treatment is chiefly directed toward imposing physical and mental rest in the most complete manner possible. The skillful use of mild sedatives frequently makes this program possible after the severe, acute symptoms have subsided. In the majority of instances, the single program of complete and protracted rest suffices to insure recovery.

ery of the patient. It is desirable for the physician to be an unhurried spectator and not to interfere with the healing forces of nature. Too often digitalis has been prescribed for coronary thrombosis but why is difficult to understand; probably because digitalis is likely to be associated with heart disease in general. The administration of digitalis under these circumstances is one of the most blatant indiscretions in its use.

When dyspnea is a prominent feature and other evidences of anoxemia are present, the use of the oxygen tent is of considerable value. Oxygen, of course, when available to the arterial blood, diminishes anoxemia and greatly relieves the strain of work on the heart.

Likewise, when dyspnea is recurrent and paroxysmal in character, cautious intravenous administration of sterile hypertonic solution of glucose is frequently of great value. The solution in concentrations of 15 to 20 per cent, in volumes of 400 to 500 c.c., is administered extremely slowly. By this method of treatment the restoration of myocardial glycogen occurs; this is an important constituent of heart muscle and one that is rapidly mobilized under conditions of anoxemia.

Under ordinary circumstances complete rest in bed must be imposed for at least five to six weeks for the myocardial infarct is only completely healed after the average period of three months. Bathroom privileges must be denied the patient during the period of rest in bed, for only too often the patient who is recovering from the effects of coronary thrombosis meets death when he rises to go to the bathroom.

PERICARDIAL EFFUSION

Pericardial effusion may constitute a cardiac emergency even though its actual onset usually is not abrupt; symptoms and signs may be alarmingly sudden in appearance. The effects of pericardial effusion on the body are essentially twofold: 1. A mechanical handicap is imposed on the heart by the presence of considerable fluid (tamponade). 2. If the effusion is the result of pericardial infection, sepsis and toxemia are coexistent.

In the great majority of instances, pericardial effusion is the result of pericarditis. The fact that the normal pericardial sac contains clear, light amber fluid in amounts of 10 to 50 c.c.

must be recalled to mind, and furthermore, it must not be forgotten that quantities less than 150 c.c. are rarely detectable by clinical methods. The fact that a definite excess of fluid may be present in the pericardial sac and yet escape detection becomes evident when one realizes the opportunity for concealment that exists. The tendency for fluid to gravitate occurs here, as elsewhere, and therefore in the absence of adhesive processes the fluid changes its position, depending on the patient's posture. Even a moderate excess of fluid may be concealed when the patient is recumbent, because it gravitates to the posterior portion of the sac.

The types of pericarditis that are associated with fluid of such an amount or of such a character as to be significant in the creation of emergencies are chiefly (1) acute purulent pericarditis, (2) acute fibrinous pericarditis, and (3) tuberculous pericarditis.

Acute purulent pericarditis occurs most frequently and accounts for approximately 68 per cent of all cases of pericardial effusion. It results predominantly from some source of intrathoracic infection such as empyema, pneumonia, acute nontuberculous pleuritis, multiple pulmonary abscesses and acute mediastinitis. Less commonly it results from hepatic abscess with rupture of the abscess into the pericardium, pulmonary emboli with necrosis of the pericardium, penetrating wounds of the pericardium, and so forth. Remote foci of sepsis in the body may eventuate in acute purulent pericarditis. Examples are found in cases of septicemia, gangrenous appendicitis with rupture of the appendix, puerperal endometritis, visceral abscesses and occasionally scarlet fever. Acute pericarditis may be associated with erosion of a pericardial blood vessel which leads to massive hemorrhage and results fatally in a relatively short time.

Treatment is concerned chiefly with the problem of a virulent infection, although many times the formation of an excess quantity of purulent fluid furnishes a mechanical cause of marked embarrassment of the heart and circulation. The length of time over which a pericardial effusion develops plays an important rôle from the standpoint of its mechanical effect. An effusion that develops rapidly and soon attains a considerable quantity is far more embarrassing to the heart than a

much greater collection of fluid that may have accumulated more slowly.

Owing to the fact that acute purulent pericarditis results chiefly from adjacent or more remote infectious processes, symptoms and signs associated with the primary process may predominate in the clinical picture and therefore may retard or prevent recognition of the infectious process. Precordial pain of considerable severity and persistence may be the first suggestive evidence of pericardial inflammation. It frequently has the general character of the pain of pleuritis, frequently is influenced by respiratory movement and occasionally coincides with cardiac rhythm. Fever is usually increased, leukocytosis augmented, dyspnea and cyanosis become evident or exaggerated, and, when fluid accumulates rapidly, the pulse rate is accelerated while the volume of the pulse is gradually diminished.

The presence of a pericardial friction rub may be the first distinctive evidence of pericarditis. Its presence may be evanescent and it may be present for a short period of time only owing to the fact that as fluid accumulates, the parietal and visceral layers of the pericardium become separated and contact between the inflamed surfaces is prevented. The area of cardiac dulness becomes increased, usually both to the right and to the left of the midsternal line and roentgenologic examination at times discloses a silhouette that is fairly characteristic evidence of the presence of fluid, the "water-bottle" shadow. This consists of bulging at the lower angles of the cardiac shadow, the region to which the fluid gravitates, and as more fluid accumulates the grooves of the heart and great vessels become filled, resulting in a rounded shadow, obliterating the characteristic delineations of the normal heart. Heart sounds become distant and when the amount of fluid in the pericardial sac is greatly increased, they may be heard with great difficulty.

It must be recalled that pleural effusion is a common finding in cases of acute purulent pericarditis and when an effusion is present in the left pleural cavity the difficulty of recognizing pericardial involvement is considerably increased.

When the pericardial effusion is recognized before it has attained proportions to hamper the heart and circulation, the

intravenous injection of sodium cacodylate frequently exhibits almost specific effects. This obviously is true only when the septic process predominantly involves the pericardium. A sterile solution of the drug is injected intravenously in doses of 5 or 8 grains (0.30 to 0.50 gm.) daily and is repeated daily; the dose is increased by 2 or 3 grains (0.12 to 0.20 gm.) each day. When definite improvement fails to become evident in three or four days, or when evidences of increased content occur, paracentesis of the pericardium is clearly indicated. Occasionally it is desirable to drain the pericardium by open section. Surgical detail is obviously beyond the scope of this discussion.

Effusion of the proportions of tamponade occurs less frequently with acute fibrinous pericarditis than with acute purulent pericarditis. In distinction to acute purulent pericarditis, the fluid associated with acute fibrinous pericarditis is non-purulent, although in some instances it may become purulent. The most common cause of this condition also is intrathoracic infection, especially acute nontuberculous pleuritis, pneumonia, and mediastinitis; less commonly, thoracic empyema, aneurysmal erosion with subsequent inflammatory extension, and rarely, cardiac infarction. Not infrequently, acute fibrinous pericarditis with effusion occurs in association with acute tonsillitis, pharyngitis or other more remote infections. The rheumatic form will not be included in this discussion as it comprises a distinct condition and one in which the accumulation of effusion rarely assumes the proportions of tamponade.

The symptoms and signs of acute fibrinous pericarditis are essentially those encountered in acute purulent pericarditis with the exception that evidences of infection are usually less severe.

The majority of patients respond remarkably to treatment with sodium cacodylate and pericardial paracentesis becomes a less frequent indication.

Tuberculous pericarditis is relatively uncommon and invariably is associated with tuberculosis elsewhere in the body. Three main types are recognized: (1) that in which effusion predominates; (2) that in which plastic exudate and resulting adhesions occur, and (3) a later stage of the second group in which fibrotic thickening and phenomena of constriction ap-

pear. This discussion is concerned with the effusive type of tuberculous pericarditis.

The fluid frequently accumulates slowly and may attain tremendous proportions with remarkably little embarrassment to the heart. I recall one patient who was ambulatory but whose pericardial sac, on paracentesis, released 1,500 c.c. of fluid. At other times, accumulation of fluid is more rapid and may require prompt paracentesis to relieve effects of tamponade.

Less commonly noninflammatory pericardial effusion constitutes an emergency. The most common cause of such effusions is congestive heart failure. However, since the advent of the newer diuretics, mobilization of retained fluids has been so prompt and effective that pericardial paracentesis under these circumstances is rarely necessary.

Very rarely, extension of malignant disease to the pericardium results in the rapid accumulation of serosanguineous fluid and paracentesis becomes imperative. However, the nature of the disease enables this procedure to be merely a palliative expedient.

STOKES-ADAMS SYNDROME

The Stokes-Adams syndrome, or convulsive syncope, is one of the most dramatic and alarming phenomena of heart disease. It frequently results in sudden death. This well-known syndrome accompanies complete heart block and is most likely to occur before complete block becomes established. At times complete heart block is abrupt in its onset and remains as a persistent disorder during the remaining lifetime of the patient, while at other times it is present only for short periods, being replaced by normal rhythm or partial heart block for varying periods of time. It is under these transitional circumstances that convulsive syncope is particularly likely to occur, although its appearance in established complete block is not unusual. Occasionally one is afforded the opportunity to observe the gradual development of disturbances in cardiac conduction occurring during the course of several years. Several times I have observed the first evidences of impairment to consist of prolongation of conduction time between the auricles and the ventricles, as disclosed by the increased P-R interval in the

electrocardiogram. This gradually became prolonged and eventuated in partial heart block (2:1 or 3:1 block) and, later, complete heart block.

Complete heart block results principally from obliterative coronary disease involving those arterial branches which supply the junctional conduction tissues; the process impairs or destroys the conductivity of the auriculoventricular (His) bundle or its two main divisions. Other causes have been found less commonly; such are gumma involving these delicate structures, calcification encroaching on the bundle, fibrosis of the bundle, fatty infiltration, lymphocytic infiltration, extension of ulcerative endocarditis and, more rarely, tumors. Occasionally infarction of the interventricular septum results in complete heart block.

The treatment of convulsive syncope probably is one of the most unsatisfactory and discouraging phases of cardiac therapy. It is palliative at best, and unsatisfactory because it is palliative and because the underlying process responsible for its occurrence cannot be removed.

Probably the most effective procedure during the attack of convulsive syncope, and when the seizures recur frequently, is subcutaneous injection of 0.23 to 1 c.c. of epinephrine in a concentration of 1:1,000. At times, oral administration of $\frac{3}{8}$ to $\frac{1}{2}$ grain (0.024 to 0.032 gm.) of ephedrine three or four times daily apparently has been helpful in reducing the frequency of the attacks, although in my experience this drug has not been perceptibly effective in the majority of cases.

Barium chloride given in doses of $\frac{1}{2}$ to 1 grain (0.032 to 0.065 gm.) three or four times daily by mouth, has been recommended. Its use is based on the premise that increased myocardial irritability results in the occurrence of ventricular premature contractions, thereby producing more frequent ventricular contractions. This result is not always achieved and frequently, when premature contractions occur, they are abortive; that is, they are incapable of accomplishing peripheral propulsion of blood and therefore are ineffectual. Barium chloride is no longer extensively prescribed.

The use of desiccated thyroid extract has definite value in reducing the frequency of attacks of convulsive syncope. It is of course, well known that the administration of active thyroid

substance in adequate dosage increases the basal metabolic rate. Increased metabolism results in an increased flow of arterial blood, brought about by the greater expulsion of blood by each contraction of the left ventricle. No appreciable increase in the rate of contraction of the ventricles occurs as the idioventricular rate of complete heart block remains within a small range of variation. Increased blood flow tends to overcome the likelihood of cerebral anemia and the increased demand on the heart seems to lessen the tendency for ventricular standstill to occur.

The administration of desiccated thyroid extract should be avoided when the presence of heart failure or impending heart failure is evident. This form of therapy should be employed only when carefully controlled determinations of basal metabolic rate are available to guide the physician in accurately establishing a safe dosage. The production of pharmacologic hyperthyroidism is to be avoided. Before beginning treatment, it is advisable to obtain basal metabolic rates on at least two consecutive days so that the patient's true metabolic level can be definitely determined. The results of treatment are invariably more satisfactory when the average metabolism is in the lower range of normal.

The initial dosage of desiccated thyroid extract is usually 1 to 1½ grains (0.065 to 0.1 gm.) daily, and later, reductions in the amount may be necessary to prevent the basal metabolic rate from attaining abnormally high levels. This form of treatment is prophylactic, has no effect on the existing attack, and in no way relieves or alters the complete heart block.

EMBOLIC MANIFESTATIONS OF HEART DISEASE

During the course of heart failure the occurrence of arterial emboli is not infrequent and in numerous instances suddenly and dramatically results in the death of the patient. Emboli occur chiefly as detached portions of mural thrombi situated either in the auricles or the ventricles of the heart. In this discussion I shall make no attempt to consider the embolic phenomena of acute or subacute bacterial endocarditis or emboli of venous origin.

Mural coagula may form in the failing heart regardless of the type of lesion responsible for the cardiopathy but they

occur with greatest frequency in association with mitral stenosis. As the heart fails and dilatation of the organ progresses, circulation becomes slowed and the amount of residual blood within the chambers of the heart increases. This status obviously favors coagulation of blood. Infection of low grade may play a part in the precipitation of this phenomenon in some cases. When auricular fibrillation is present the tendency for auricular thrombi to form greatly increases owing to the fact that the chambers become adynamic, no longer contract, and consequently their filling and emptying become passive rather than active functions. If loosely formed or attached thrombi are present the chance for detachment of particles is very great. This is also favored by the establishment of normal rhythm in cases of auricular fibrillation. Likewise, when the heart appears to be improving its function, contraction becoming more adequate and circulation improving, portions of thrombi are swept into the systemic or pulmonic circulation.

The chambers where thrombi are formed do not necessarily coincide with that portion of the heart predominantly involved by the underlying disease. For example, in a heart failing from hypertension, the formation of mural thrombi may not be limited to the left auricle or ventricle but may occur in either chamber on the right side of the heart.

When a thrombus becomes detached from the left side of the heart and the embolus gains entry to the systemic blood stream its ultimate destination is conjectural. However, clinical experience indicates that an order of predilection occurs. The spleen appears most frequently to be the destination for emboli; other destinations in order of frequency are the brain, kidneys and other parenchymatous abdominal viscera, the extremities, predominantly the legs, the intestines and the heart (coronary embolism). Emboli which arise from the right auricle or ventricle inevitably reach the lungs with the exception of the rare cases of paradoxical embolism, in which intussusception permits the embolus to gain entrance to the systemic blood stream. When the parenchymatous organs and the heart are invaded suddenly by emboli, infarction occurs: when main arterial tributaries in the extremities and the intestines are occluded, gangrene develops.

Complete or partial recovery depends on the structure involved and the extent and degree of deprivation of circulation that results. For example, the spleen, kidneys, and lungs tolerate remarkably one or more embolic insults with unusual restitution of function. Likewise, the brain may recover remarkably if the occlusion has not been massive and if vital areas have escaped involvement. It is not unusual for a patient afflicted with embolic hemiplegia to recover and have only slight residual weakness of the affected arm and leg. Massive cerebral infarction, of course, eventuates in death in a relatively short time. Mesenteric embolic occlusion almost invariably results in death.

If emboli are carried to the extremities and gangrene subsequently develops, usually a fatal outcome occurs because amputation is attended by grave risk owing to the patient's serious general condition. It must be borne in mind that emboli may be multiple, arriving at various destinations within a brief period of time.

Emboli, regardless of their destination, are associated with an abrupt onset of severe and persistent pain, corresponding in general with the part involved. Dyspnea, cough and hemoptysis are the usual symptoms of pulmonary embolism, and when infarction is extensive and recurrent, icterus may appear. Gross or microscopic hematuria aids materially in identifying renal infarction. Signs of shock and collapse frequently accompany massive arterial occlusion.

The treatment of arterial embolism consists primarily of complete rest and relief of pain. The latter is best accomplished by subcutaneous administration of adequate amounts of morphine. When pulmonary infarction occurs, placement of the patient in an oxygen tent frequently confers greater comfort and lessens the load on the circulation by facilitating the availability of abundant oxygen.

If an embolism exists in an extremity or a mesenteric vessel, the possibility of embolectomy must not be overlooked and immediate surgical consultation occasionally may permit an operative procedure to be performed successfully.

Usually, when sudden arterial occlusion occurs, considerable associated spasm in contiguous arteries occurs, which, if not promptly abolished, may lead to more extensive throm-

days, finally becoming stable when the volume of blood is restored to normal.

The blood picture of acute posthemorrhagic anemia is one which reflects increased regenerative activity of the bone marrow. Within a few minutes after the onset of the hemorrhage an increase in the blood platelets in the peripheral blood occurs. This is followed in the course of four or five hours by neutrophilic leukocytosis. When the demand upon the bone marrow is particularly acute, immature leukocytes may be thrown into the peripheral circulation in large numbers. Myelocytes, promyelocytes, and even myeloblasts may be observed (leukemoid reaction). On the second or third day after the onset of the hemorrhage the reticulated erythrocytes in the peripheral blood begin to increase, reaching a peak between the fourth and eighth days; they then usually decrease to a level somewhat in excess of normal, but in those cases in which bleeding continues over a period of several days, the percentage may remain relatively high. Other signs of regenerative activity, such as polychromatophilia and normoblastosis, are present. As the percentage of reticulated erythrocytes falls, hypochromasia appears, for as a rule the regeneration of hemoglobin lags behind that of erythrocytes. In the event of prolonged bleeding, microcytosis of erythrocytes also develops.

After a severe hemorrhage, the peripheral blood gradually returns to normal in from four to eight weeks. Recovery may be retarded when the iron stores in the body are depleted, when the diet is deficient in iron, or when chronic infection is present within the body.

In most cases the clinical history will reveal the source of the hemorrhage. More rarely, the source of the hemorrhage may be obscure but the picture of the illness may suggest acute loss of blood. Recently we had a case in which considerable bleeding into the gastro-intestinal tract had escaped the notice of the patient. Symptoms of progressive weakness and pallor had developed over a period of two weeks. Tarry stools had been observed following the administration of iron elsewhere. Leukocytosis and severe anemia were present. Examination of the blood disclosed hypochromasia, signs of markedly increased regeneration of the erythrocytes, and myeloid immaturity to the stem cells. A tentative diagnosis of acute myel-

ogenous leukemia was made but, because the signs of erythrocytic regeneration and the increase in blood platelets were out of proportion to those usually observed in leukemia, acute loss of blood associated with a leukemoid reaction was suspected. Roentgenologic examination revealed a duodenal ulcer. Treatment for the ulcer was instituted and the patient made a complete recovery, the blood returning to normal in about six weeks. None of the usual symptoms of ulcer could be elicited in this case, even after the presence of the ulcer had been discovered, although the fact was brought out later that the patient had vomited blood on one occasion. This case, therefore, emphasizes the diagnostic value of careful study of the blood smear in cases in which there has been an acute loss of blood. Other obscure causes of acute loss of blood are "silent" carcinoma of the gastro-intestinal tract, tumor and ulcer of the small bowel, ulcer of Meckel's diverticulum, and polypoid lesions of the stomach or intestines.

In all cases in which acute hemorrhage occurs it is advisable to study the blood in order to eliminate a dyscrasia as the cause of the bleeding. Examination of blood smears, which must be properly made and stained, is in our opinion the most valuable of the available tests and should never be omitted. The presence of large numbers of stem cells and immature leukocytes in the film of blood immediately establishes the diagnosis of acute leukemia, if a leukemoid reaction can be excluded; an absence or marked paucity of blood platelets in the smear, when the platelet count should be increased, suggests acute thrombocytopenic purpura; and an absence of signs of erythrocytic regeneration, associated with low leukocyte, erythrocyte, and platelet counts, is indicative of acute aplastic anemia. Other tests, such as a platelet count and a determination of the bleeding time, coagulation time, clot retractility, and prothrombin time, also are of value when the presence of an acute blood dyscrasia is suspected.

The immediate treatment of acute loss of blood consists obviously in an attempt to control bleeding and in an attempt to replace the diminished volume of blood with fluid. Blood is the fluid of choice, for it not only helps to restore the volume of blood, but supplies erythrocytes, hemoglobin, blood platelets and other factors concerned in coagulation. Indications for

blood transfusion are signs of a decreased blood volume and a rapidly falling erythrocyte count. In emergencies, while arrangements are being made to give the patient a transfusion, it is usually advisable to administer physiologic saline solution, 5 per cent d-glucose solution, or 6 per cent acacia solution, intravenously. A satisfactory solution of acacia can now be obtained commercially ready for administration.

The quantity of blood and the rate at which it is given depend upon the source of the bleeding. In cases of hemorrhagic diathesis, for example, in which there is ubiquitous oozing from the mucous membranes and into the skin, the administration of 500 c.c. or more of blood may result in a cessation of bleeding before the transfusion has been completed. On the other hand, in the presence of a bleeding duodenal ulcer, the administration of smaller quantities (250 c.c.) of blood, given slowly so as not to raise the blood pressure and start the bleeding again, is a wise procedure. In these cases repeated small transfusions may be given or the continuous drip method of transfusion may be resorted to, giving 1,000 or even 2,000 c.c. in twenty-four hours. In addition to transfusions the administration of fluids intravenously, subcutaneously, by proctoclysis, and, when not contraindicated, by mouth, is advisable. During convalescence from acute loss of blood, patients should be given diets rich in iron and animal protein to facilitate regeneration of hemoglobin and plasma proteins. The administration of iron is theoretically of doubtful value in uncomplicated cases of acute blood loss, but it should be given in those cases in which chronic bleeding has occurred prior to the acute hemorrhage, for in such cases the body stores of iron usually have been depleted.

Loss of blood in essential hematuria and functional menorrhagia has been very effectively treated by the administration of moccasin venom. For details concerning this method of treatment the reader is referred to papers by Watkins,³⁰ Watkins and Thompson, and Watkins and Mussey.

THE HEMOLYTIC ANEMIAS

Increased destruction of blood is evidenced by an increase in the quantity of pigments derived from hemoglobin in the blood plasma and in the feces, the appearance of these pig-

ments in urine, jaundice, and signs in the peripheral blood of increased regenerative activity of the bone marrow. Hemoglobin may appear unchanged in the urine when the process of hemolysis is extraordinarily rapid.⁵ Values for hemoglobin and erythrocytes fall in proportion to the rate of blood destruction. The color index remains at or near unity. The leukocytes and blood platelets usually are increased in number. Examination of stained blood films discloses large numbers of reticulated erythrocytes, polychromatophilia, anisocytosis, nucleated erythrocytes, and, more rarely, younger forms of the erythrocytic series. Leukemoid reactions of the myelogenous type are not uncommon.

Episodes of markedly increased blood destruction are known clinically as "crises." The severity of the process of hemolysis is subject to wide fluctuation in different cases, being dependent on constitutional as well as etiologic factors. It is not rare, however, to see patients who have become critically ill in the course of from twenty-four to seventy-two hours. The treatment in such cases must be prompt and must be based primarily on a knowledge of etiology. Increased hemolysis may be due to extrinsic or intrinsic factors:

Hemolytic Anemias due to Extrinsic Factors.—1. *Infection.*—Increased destruction of blood is not uncommon in infections of various kinds but it is usually of minor significance. It is more marked in those instances in which the blood stream is invaded, as in septicemia due to the hemolytic streptococcus for example. Hemolytic anemia of severe degree may develop rapidly in the presence of infection due to *Bacillus welchii*. In these instances, however, the anemia is of minor importance when compared with the infection with which it is associated, and rarely is the anemia itself severe enough seriously to endanger life.

In malaria, increased hemolysis occurs but the anemia that develops ordinarily is not severe. More rarely, and especially in blackwater fever, crises may occur, sometimes being so severe as to cause hemoglobinuria.

Bartonella bacilliformis infection, in man known as "Oroya fever" and reported chiefly in western South America, is an acute infectious disease characterized by an extremely severe hemolytic anemia, leukocytosis, and fever. Spontaneous re-

covery, despite the severity of the hemolytic process, is the rule. Clinically the picture is similar to that of the acute hemolytic anemia of Lederer.

2. *Chemicals and Drugs*.—A large number of chemical substances cause excessive destruction of erythrocytes; these are principally occupational hazards. Such substances include phenylhydrazine, aniline, nitrobenzol, trinitrotoluol, potassium chlorate, and a host of others.

Recently, reports have appeared in the literature of the development of acute hemolytic anemia in patients who have been given the drug sulfanilamide. Recovery in each instance promptly followed withdrawal of the drug, although in some cases transfusions also were given to expedite recovery. Harvey and Janeway have called attention to the resemblance of this type of anemia to the hemolytic crises produced by phenylhydrazine. They advocated the taking of blood counts of patients receiving large doses of sulfanilamide throughout the period of treatment and prompt withdrawal of the drug in the event that anemia develops.

3. *Allergy*.—That allergy may be a factor in the causation of increased destruction of blood now seems to be definitely established, and this is typified by favism.^{14, 19, 20} Favism is an acute hemolytic anemia with hemoglobinuria which develops following ingestion of the bean, *Vicia fava*, or inhalation of pollen from the plant in blossom. It occurs in a small proportion of the population in regions where the *Vicia* bean is grown, chiefly in southern Italy, Sicily and Sardinia. Isolated cases have been reported in Germany, but as far as we are aware only two case reports have appeared in the American literature; McCrae, however, has stated that several unreported cases have come to his attention. The hemolytic reaction is thought by some to represent a hypersensitiveness to the protein in the bean, the various manifestations being the result of anaphylaxis.

The condition must be differentiated from other hemolytic anemias severe enough to cause hemoglobinuria: malaria paroxysmal hemoglobinuria, and Lederer's anemia. When there is a history of ingestion of the fava bean, or a family history of recurrent attacks of jaundice and severe anemia the diagnosis is not difficult.

The most important single item in the treatment of hemolytic anemias due to extrinsic factors is removal of the cause of increased hemolysis. In most instances the cause of the destruction of blood can be readily determined and, after withdrawal of the harmful agent, recovery is spontaneous. However, transfusions may tide the patient over the period of the crisis and prevent his dying of severe anemia until the defense forces of his body have been mobilized. During recovery the administration of a diet rich in animal protein, vitamins, and iron is advisable though not essential.

In favism the therapeutic measures usually recommended consist of epinephrine for the early manifestations of shock, and blood transfusions for the anemia. The blood count, of course, should be followed closely until the hemoglobinuria disappears and the values for hemoglobin and erythrocytes begin to rise. A high vitamin diet and the administration of iron also may be helpful during the recovery phase. Once the relationship of the hemolytic process to the Vicia bean is established, the patient should be warned to eliminate the bean from his diet and to avoid the plant in blossom.

Hemolytic Anemias due to Intrinsic Factors.—1. *Acute Hemolytic Anemia*.—This is a type of anemia, first described as a separate entity by Lederer^{17,18} in 1925, which affects both sexes and occurs most commonly in from the second to the fourth decade of life, although it may develop at any age. The occurrence of this type of anemia is common enough to warrant detailed description. The cause of the condition is unknown. Lederer thought that the etiologic agent most likely was infectious, but blood cultures and tissue cultures taken at necropsy have been sterile. The erythrocytes should be examined for inclusions because of similarity to Bartonella infection.

The disease is characterized by an acute onset with chills, fever, headache, gastro-intestinal symptoms (anorexia, vomiting, diarrhea), weakness, and rapidly developing pallor and jaundice. Abdominal pain may be present, and one case has been reported in which the location and severity of the pain simulated appendicitis (Parkes-Weber). Severe prostration occurs; mental confusion, coma, and even paralysis may develop. Hematuria, hemoglobinuria, hematemesis, purpuric manifestations, and retinal hemorrhages have been observed

in severe cases. The spleen and liver may or may not be enlarged.

The blood picture is characterized by a rapid fall in the values for erythrocytes and hemoglobin, the former often dropping below 1,000,000 cells per cubic millimeter within a few days. There is a tendency to macrocytosis, although microcytes may be present. The color index usually remains about 1. Regeneration of erythrocytes is greatly increased, large numbers of reticulated and nucleated erythrocytes appearing in the peripheral blood. There is usually an associated leukocytosis, which not infrequently is quite high, and a leukemoid reaction of the myelogenous type may be observed. Leukocyte counts should be corrected so that the large number of nucleated erythrocytes in the circulation are not included in the leukocyte counts or leukemia may be suspected. Sometimes, the leukocyte count may not be elevated, and in rare instances leukopenia has been observed. The blood platelets are normal. The fragility of erythrocytes in hypotonic salt solution usually is normal, but instances of a slight increase in fragility in the active phase of the anemia have been reported. The van den Bergh reaction is indirect and the amount of bilirubin in the serum is increased. Increased quantities of urobilin are found in the feces and urine. Hemoglobinuria has been observed in some cases. The prognosis in untreated cases of acute hemolytic anemia of the Lederer type may be grave, and recognition of the condition is therefore most important. In cases in which treatment is carried out the prognosis is favorable.

Treatment consists solely of blood transfusions, and these should be continued until the hemolytic process ceases. Not infrequently the response to a single transfusion is dramatic and is followed by the patient's complete recovery. Liver therapy has been employed, but its value as a therapeutic agent in this disease has not been established.

2. *Familial Hemolytic Icterus*.—Familial hemolytic icterus is a disease which fundamentally is characterized by constitutional abnormalities of the erythrocytes, namely, spherocytosis and an increased fragility in hypotonic saline solution. These specific characteristics of the erythrocytes are present at birth and continue throughout life, even after splen-

nectomy. This abnormality exists in a latent as well as in an active form. In the latent form there are physical abnormalities in the erythrocytes but no significant alteration in the rate of blood destruction. In the active form, increased hemolysis occurs, and this is subject to wide fluctuations. Cases are encountered in which the attacks of jaundice are of short duration and the anemia mild; in other cases "crises" develop with alarming rapidity in patients previously showing only mild degrees of increased hemolysis; in still other cases the jaundice may be persistent and the anemia severe for long periods of time. Cases falling into the last two groups obviously constitute emergencies, although they seldom end disastrously.

Crises may develop spontaneously or be precipitated by various factors such as infection, overexertion, exposure to cold, or increased altitude. The onset is characterized by rapidly increasing icterus, nausea, vomiting, and fever. Leukocytosis and severe anemia develop and bile pigments appear in the urine. Though alarming, the attack seldom is fatal; as recovery takes place the values for erythrocytes and hemoglobin rise almost as rapidly as they fell at the onset of the crisis.

The spleen is enlarged in almost all cases. During a crisis it may enlarge rapidly and the patient may complain of pain in the left upper quadrant. As the attack subsides, the spleen diminishes in size and may even recede temporarily behind the costal margin.

Examination of the peripheral blood discloses those features characteristic of an overactive bone marrow. The erythrocyte count rarely falls below 2,000,000 cells per cubic millimeter except during crises, when it may fall below 1,000,000; during remissions it may become normal. The reticulated erythrocytes almost invariably are increased and may reach very high levels. The values for leukocytes and blood platelets usually are elevated in the presence of increased hemolysis. In the average case examination of blood films discloses marked anisocytosis, the majority of erythrocytes being spherical microcytes which stain more deeply than the larger cells. The remainder of the erythrocytes may be normal in size or slightly larger than normal; they usually show polychromatophilia and considerable nucleation, especially when destruc-

tion of blood is going on at an increased rate. Haden and others have shown that the mean diameter of the erythrocytes in this disease is less than normal, the calculated thickness greater than normal, and the mean corpuscular volume normal or increased. The blood volume is normal (Giffin and Brown). The fragility of the erythrocytes to hypotonic salt solution is increased. The value for serum bilirubin is above normal and the van den Bergh reaction is indirect. A history of jaundice, anemia, or splenomegaly in other members of the family is of considerable diagnostic importance.

In familial hemolytic icterus the abnormally fragile erythrocytes are destroyed at an increased rate, principally in the spleen. Except in rare instances splenectomy results in cessation of the hemolytic process. Splenectomy, even for patients in the latent stage of the disease, probably is justified in view of the risk these individuals run of getting into difficulty later in life. Doan, Curtis, and Wiseman^{2,3} recently have demonstrated that splenectomy can be successfully performed during a hemolytic crisis. According to the older teachings, splenectomy was thought to be contraindicated during a hemolytic crisis and transfusions were resorted to when the anemia was severe; however, preoperative transfusions are likely to be followed by severe reactions in hemolytic icterus. Death during a crisis is not common but does occur. Doan and his associates, however, have found that there is an immediate increase of 500,000 erythrocytes per cubic millimeter following removal of the spleen, the patient in a sense transfusing himself. They therefore claimed that delay was unnecessary and that splenectomy during a crisis might be a life-saving measure. Our recent experience leads us to agree with these conclusions, but we feel that, in severe crises, it is important to give transfusions immediately after splenectomy.

3. *Sickle Cell Anemia*.—This is a form of hemolytic anemia which in many respects (familial incidence, constitutionally abnormal erythrocytes, tendency to remissions, and relapses) resembles familial hemolytic icterus.¹⁶ It is present almost exclusively in Negroes and is transmitted as a mendelian dominant. It occurs mainly in the first two decades of life, very rarely after the age of thirty, and shows no essential sex preference.

Like familial hemolytic icterus, there are latent and active forms. In the active form the values for hemoglobin and erythrocytes, although usually low, assume fairly constant levels which from time to time are broken by crises of hemolysis. In the latent form the physical characteristics of the erythrocytes are abnormal, but there is no increase in blood destruction. About 7 per cent of Negroes show the sickling phenomenon, but in only a small proportion of these does anemia develop.

Individuals suffering from this disease frequently complain of episodes of weakness, fatigue, and other symptoms suggestive of anemia; or they may give a history of attacks of severe abdominal pain which may closely simulate various acute abdominal conditions. Vomiting may occur. Stiffness and aching pains in the muscles and joints are not infrequently experienced and leg ulcers are common. Physical examination often discloses evidence of malnutrition. The spleen is palpable in a small proportion of cases and superficial adenopathy sometimes is noted. Fever may be observed.

The blood picture is characteristic: The erythrocytes possess a marked tendency to assume abnormal shapes, and oval, oblong, spindle, and crescent or sickle-shaped cells may be observed. When the degree of anemia is mild, sickle-shaped erythrocytes may be sparse in fixed smears. The phenomenon of sickling is increased in the absence of oxygen and can be readily demonstrated in sealed cover-slip or hanging-drop preparations of fresh blood. The blood picture otherwise shows those features characteristic of increased hemolysis and an increased demand upon the bone marrow. The occurrence of hemolytic anemia in a Negro should immediately suggest the possibility of sickle cell anemia.

There is no specific treatment for this disease. During crises it may be necessary to resort to transfusions. Splenectomy has been performed in a limited number of cases of this disease but the value of the procedure has not been firmly established. Haden and Evans reviewed the literature and observed that those patients whose spleens were found to be large at the time of removal received the greatest benefit from the operation. Since the disease is a hemolytic disorder, they felt that splenectomy is indicated when the spleen is enlarged.

Adequate diets and iron therapy should be given in all cases in order to promote maximal blood formation.

4. *The Paroxysmal Hemoglobinuria*.—An excellent review of the hemoglobinurias has been published by Witts, and the reader is referred to this paper for a detailed account of the subject. Three types of paroxysmal hemoglobinuria which recur in paroxysms as a result of intravascular hemolysis and hemoglobinemia may be distinguished, namely, the cold, the march or exertion, and the nocturnal forms. A fourth type, formerly termed "paralytic hemoglobinuria," does not belong in this category because the discoloration of the urine which occurs is due to myoglobin rather than to hemoglobin.

Symptoms common to all forms of paroxysmal hemoglobinuria, regardless of cause, are shock, anemia, oliguria or anuria, and thrombosis in various parts of the vascular tree. The onset of a paroxysm may be characterized by generalized aching pains, abdominal cramps, headache, and malaise, followed by a severe chill and fever. Jaundice may occur; when present the van den Bergh reaction is indirect except in severe cases in which it may become direct and bile may be excreted in the urine. The number of leukocytes and platelets in the blood falls at the onset of the attack but later may increase. Regeneration of the erythrocytes is rapid except in cases of prolonged hemolysis. The usual signs of regeneration may be observed in the blood smears, and in the blood during the paroxysms. The urine passed during a paroxysm contains oxyhemoglobin and methemoglobin, and various other pigments derived from hemoglobin, albumin, and, in some cases, granular and red cell casts. Death is said to occur if the free hemoglobin in the plasma exceeds 3 per cent. On the other hand, paroxysms may be so mild that they are unattended by constitutional symptoms.

In the United States the term "paroxysmal hemoglobinuria" is in general used to connote only one type of hemoglobinuria, the "cold" variety. It is advisable, however, to add the qualifying adjective since "cold" hemoglobinuria differs from the "march" and "nocturnal" forms. Paroxysmal cold hemoglobinuria occurs in individuals in whom evidence of syphilis almost always can be demonstrated; it is due to sensitization of the erythrocytes to hemolysins in the circulating

blood which under special circumstances, and especially after exposure to cold, results in destruction of erythrocytes with the consequent excretion of hemoglobin and its derivatives in the urine. The attacks can be induced by immersing the hands or feet in ice water for from ten to twenty minutes, and this procedure is the basis for the Rosenbach and Ehrlich tests. The Wassermann test is said to be positive in about 90 per cent of the cases. A positive Donath-Landsteiner reaction is diagnostic. Antisymphilitic treatment in most cases is followed by the disappearance of the paroxysms.

Paroxysmal march hemoglobinuria³⁴ differs from paroxysmal cold hemoglobinuria in that the former bears no relationship to syphilis, exposure to cold, or to the presence of the autohemolysin of Donath and Landsteiner. The sole causative agent of the paroxysms of hemolysis seems to be exertion. It is a relatively harmless abnormality and may disappear in adult life. There is no specific treatment other than avoidance of strenuous exercise.

The third form of paroxysmal hemoglobinuria is the nocturnal variety which is associated with a chronic hemolytic anemia.¹² It occurs more frequently in males than in females, the first symptoms usually appearing in the third or fourth decade of life. The disease usually begins insidiously with the development of a hemolytic anemia, which, when fully established, is characterized by paroxysms of hemoglobinuria and the persistence of increasing blood destruction and anemia between the attacks. The paroxysms commonly occur at night. When the attack is mild, the urine voided during the day may be free of hemoglobin; when severe, the hemoglobinuria may last days or weeks but is usually more intense at night. The cause of the paroxysms is unknown. The mean corpuscular volume of the erythrocytes is within normal limits, spheromicrocytosis is absent, and the fragility is normal or slightly increased; the condition can thus be differentiated readily from the crisis of familial hemolytic icterus.

There is no specific treatment for this nocturnal form of paroxysmal hemoglobinuria. The patient may live for many years with the malady. Splenectomy has been performed, but it is an extremely hazardous procedure and does not result in cure. Transfusions are generally followed by untoward reac-

tions and they may precipitate attacks of hemoglobinuria; they are definitely contraindicated when the anemia becomes profound. In severe paroxysms, when the values for hemoglobin and the erythrocyte count drop to alarmingly low levels and the condition of the patient becomes critical, the administration of acacia solution intravenously is advisable to help maintain blood volume. Between attacks of hemoglobinuria and during recovery from a paroxysm the anemia should be treated by the use of such measures as adequate diet, administration of preparations of iron by mouth, and intramuscular injections of liver extract.

5. *Indeterminate Hemolytic Crises.*—There is one very rare type of hemolytic anemia which is not related to any of the previously mentioned hemolytic diseases, and this is known as "acute hemolytic crisis."²⁹ The etiology is unknown but the precipitating factor is a blood transfusion, given usually for the control of hemorrhage, anemia, infection, or some other condition unrelated to a primary blood dyscrasia. In our experience this condition has occurred only in recipients with a blood grouping of 2A and has been independent of the group of donor, whether group 2A or 4O. In no case has there been any evidence of hemolytic anemia before precipitation of the crisis and, after recovery, all tests of the blood have been normal. The typical findings are the occurrence of jaundice, a progressive and rapidly developing anemia, and leukocytosis with a leukemoid reaction; in severe cases this reaction is so marked that it may be confused with acute myelogenous leukemia. A marked increase in the regeneration of erythrocytes, spherical microcytosis, and rapid enlargement of spleen and liver are present. In one case four transfusions were given before the condition was recognized, the transfusions being given for postoperative oozing from the nasal septum. The initial blood count showed 70 per cent hemoglobin and 4,480,000 erythrocytes and 7,900 leukocytes per cubic millimeter. Following each transfusion there was increased jaundice and hemolysis, so that after the fourth transfusion, the liver was enlarged below the navel and the spleen reached to the pelvic brim. A blood count revealed 12 per cent hemoglobin, 450,000 erythrocytes, and 78,000 leukocytes. Fragility of the erythrocytes was increased. After recovery the blood returned

to normal, the spleen and liver were not palpable, and a fragility test was normal. There has been no recurrence.

Treatment of this condition obviously lies in its early recognition and in distinguishing it from an acute crisis of congenital icterus, in the administration of fluids intravenously, and in avoidance of transfusions. In severe crises splenectomy may be advisable, but in our experience the patients have recovered without operation.

ACUTE APLASTIC ANEMIA

This is an idiopathic disease which is characterized by progressive anemia, leukopenia, and thrombocytopenia and which progresses to a fatal termination in a few weeks or months. Studies of the bone marrow after biopsy or at necropsy in some cases show atrophy of the hematopoietic areas and their replacement with fatty and gelatinous connective tissue, in other cases hyperplasia of the red marrow. In cases in which a hyperplastic marrow is found it is assumed that the end stages of cell maturation have been arrested and that immature cells are not being released into the circulation.

The disease occurs mainly in young adults between the ages of fifteen and thirty and it affects females more frequently than males. The symptoms at first are mainly those of anemia. Later in the course of the disease infections are common; these develop as the granulocytes disappear from the blood stream. When the platelets fall to low levels, hemorrhages occur. Examination of blood smears fails to disclose signs of erythrocytic regeneration. The erythrocytes are practically normal in appearance. The reticulated erythrocyte counts are usually at a low normal but may in some cases be slightly increased. Aplastic anemia should not be confused with agranulocytosis for, in the latter, there is no anemia. Likewise, the leukopenia and the lack of regeneration of erythrocytes differentiates this condition from thrombocytopenic purpura. In doubtful cases biopsy of bone marrow may be of value in establishing the diagnosis, although the utilization of this procedure rarely should be necessary. There is no specific treatment for aplastic anemia. Blood transfusions are only of temporary benefit for the disease ultimately is fatal. They may, however, considerably prolong life.

PERNICIOUS ANEMIA

Emergencies rarely are encountered nowadays in cases of pernicious anemia because the disease generally is recognized early and effective treatment is instituted before the anemia becomes profound. Only occasionally does the physician see patients whose erythrocyte count is near or below 1,000,000 per cubic millimeter. The adjustment to the anemia and the endurance which some of these patients exhibit is often phenomenal. Recently a patient walked into the office who had an erythrocyte count of 700,000 per cubic millimeter.

As a general rule it is advisable to hospitalize all patients with pernicious anemia whose erythrocyte count is less than 1,500,000 per cubic millimeter before instituting liver therapy. During the first two or three days after beginning the administration of liver extract the erythrocyte count will drop frequently by 200,000 to 400,000. Whether this is due to a shift in fluid balance between the tissue spaces and blood stream, resulting in hemodilution, has not been determined. The drop in erythrocytes, however, may be sufficient to produce signs of collapse and impending death from anemia. Erythrocyte counts should be made daily after treatment has been begun and should be continued until the level of erythrocytes begins to rise. While transfusions are not ordinarily necessary in the treatment of pernicious anemia, they should be given immediately in all cases in which the erythrocyte level drops to critically low levels and signs of insufficient oxygen carriage appear. The administration of transfusions to these patients is not without danger for untoward reactions or pulmonary edema may develop. There is less likelihood of complications arising, however, if the blood is kept warm and given slowly; not more than 300 c.c. should be given at one time. The administration of a small amount of blood may result in marked improvement. When necessary, a second small transfusion may be given within a few hours. If signs of circulatory failure develop, cardiac stimulants and epinephrine should be administered.

When patients with pernicious anemia are in a severe relapse, it is advisable to administer liver extract parenterally in large doses when the treatment is first instituted. It is our custom at the Clinic to administer an initial dose several times

that known to induce a maximal response in the reticulated erythrocytes, for it has been our experience that recovery is more prompt in these cases than in those in which smaller doses of liver extract have been given parenterally or in which oral therapy has been employed.

POLYCYTHEMIA VERA

In cases of polycythemia vera emergencies occasionally arise which may be dependent upon the disease itself or the result of poorly controlled or too vigorous treatment. Cerebral manifestations of syncope, disorientation, deterioration, or acute mania may result from impaired cerebral circulation. Thrombosis of vessels may occur in any location, resulting in findings indicative of cerebral accidents, acute abdominal conditions, coronary occlusion, or gangrene.

Polycythemia vera is characterized by an erythrocyte count of 6,000,000 to 9,000,000 per cubic millimeter or more, a definitely increased blood viscosity, an increased hematocrit percentage, and an increased whole blood volume. In the preparation of blood smears the cells spread poorly because of the high viscosity; this, together with evidence of increased regeneration of erythrocytes, may aid in the diagnosis. Myeloid immaturity may be present, even to the degree which might suggest leukemia. Physical examination usually discloses the characteristic plethoric appearance, with erythrosis and splenomegaly. Engorged retinal vessels are present. Relative polycythemia of congestive heart failure, emphysema, and related conditions are differentiated by identification of the underlying disease and the presence of a normal or only slightly increased blood volume.

In addition to symptomatic treatment for the local emergency, immediate treatment of the polycythemia should be instituted. Emergency treatment consists primarily in repeated phlebotomy to lower the volume and viscosity. An occasional patient has to be bled of a liter or more at the onset of the emergency treatment; 500 c.c. of blood should then be removed every second or third day until the hematocrit reading reaches a normal level. Phenylhydrazine therapy should then be instituted. It has been found that thrombosis is much more likely to occur if phenylhydrazine is used before the hematocrit

value is reduced to approximately normal. Doses of 0.1 mg. of phenylhydrazine hydrochloride may be given three times on one specified day each week (that is, 0.3 mg. per week); the dose has to be adjusted to the individual case and determined by repeated checks of the erythrocyte count and hematocrit value. Too vigorous treatment with phenylhydrazine results in signs of excessive hemolysis; in extreme cases, there may be progressive aplasia of the marrow with anemia or pancytopenia. All medication should be stopped until the marrow recovers sufficiently to carry on; recovery may be spontaneous or transfusion may be necessary. Yellow bone marrow extract and liver extract may be used to aid in stimulating activity of the marrow.

ACUTE LEUKEMIA

The chief problem confronting the physician who sees a patient with a rapidly progressing anemia, weakness, fever, and with hemorrhagic phenomena is that of diagnosis since acute leukemia, acute plastic anemia, and acute thrombocytopenic purpura may be indistinguishable clinically. There is no known specific treatment for acute leukemia or for acute aplastic anemia, but the patient with essential thrombocytopenic purpura may be permanently benefited by supporting him with transfusions during the acute stage of thrombocytopenia and by performing splenectomy during the subsequent remission.

An elevated leukocyte count is not always essential to the diagnosis of leukemia; one of us²⁷ previously reported that approximately 45 per cent of the cases of acute leukemia seen at The Mayo Clinic from 1929 to 1933 had total leukocyte counts of less than 10,000 per cubic millimeter. It is the qualitative rather than the quantitative picture that is important. Morphologically the finding of large numbers of immature leukocytes with a high proportion of "stem cells" (myeloblasts) in stained films of blood establishes the diagnosis.

On the basis of the morphologic characteristics of the cells in the blood, the leukemias may be divided into the lymphatic, myelogenous, monocytic, and reticulo-endothelial varieties. In the last named, termed "acute leukemic reticulo-endotheliosis," cells of reticulo-endothelial origin which are more primitive than stem cells are observed in the circulating blood. Acute

monocytic leukemia may be subdivided further into two types, namely, the Schilling type and the Naegeli type. In the former, transitions from reticulo-endothelial cells to monocytes may be distinguished; in the latter, intermediate stages between myeloblasts and monocytes may be seen. The Schilling type of monocytic leukemia, therefore, may be considered a variant of leukemic reticulo-endotheliosis, the Naegeli type a variant of myelogenous leukemia. These problems are of considerable academic interest but are of secondary clinical importance.

The anemia which is an invariable accompaniment of acute leukemia usually is normocytic and normochromic, except in late stages of the disease when hypochromasia may be observed. Not infrequently macrocytosis of the erythrocytes may be present. Signs of increased regeneration of the erythrocytes are the rule. Thrombocytopenia, prolonged bleeding time, normal coagulation time, and prolonged clot retraction are found in most cases, features which also are common to essential thrombocytopenic purpura and acute aplastic anemia.

The differential diagnosis is not difficult if a few facts are kept in mind. In acute aplastic anemia, the spleen is not palpable, there is a progressive fall in the leukocyte count as well as in the values for erythrocytes and platelets, and an absence of immature leukocytes and of signs of increased regeneration of erythrocytes in the peripheral blood. Moreover, considerable temporary benefit may be derived from transfusions, a feature not observed as a rule in cases of acute leukemia. In essential thrombocytopenic purpura, there is often a history of remissions and relapses, a slight to moderate leukocytosis during exacerbations when hemorrhagic phenomena are present, absence of splenomegaly, and absence of young leukocytes in the circulating blood. Occasionally one encounters cases of acute thrombocytopenic purpura with severe hemorrhagic manifestations in which small numbers of immature leukocytes and even myeloblasts are present in the blood; these disappear as the patient recovers from the exacerbation. Such leukemoid reactions enhance the difficulties of diagnosis, since the picture may be confused with that of leukemia. However, in acute leukemia, the percentage of young forms, and particularly stem cells, is much greater than that observed

in most leukemoid reactions and this difference is usually sufficient for one to interpret the morphologic picture correctly.

The treatment of the acute leukemias is at best palliative and consists principally in the administration of transfusions. Exposure to roentgen rays and radium is contraindicated, for this usually aggravates the anemia and hemorrhagic features and may cause more marked immaturity of the leukocytes and more infiltration of the bone marrow and other hematopoietic organs.

GRANULOCYTOPENIA

Granulocytopenia immediately constitutes an emergency, whether in the early stage of fatigue or in the late septic stage. If the blood smear reveals a state of absolute granulocytopenia, death usually ensues within seven days unless granulopoiesis recurs.

Granulocytopenia may be classified as primary or secondary. Reported pathologic studies of the bone marrow show that either the production of all granulocytic elements has ceased, leaving a bone marrow devoid of these cells, or that there has developed a hyperplastic marrow filled with young cells unable to mature as functional elements of defense. This latter condition of the granulocytes is analogous to that of the erythrocytes in pernicious anemia. Secondary granulocytopenia differs from the primary form only in its mode of production; it carries essentially the same prognosis. Certainly if the condition can be diagnosed as secondary and the cause removed, the prognosis should be better, but when seen in late stages and when secondary invaders cause rapid dissolution, the removal of the etiologic agent is but a gesture. Careful inquiry concerning the use of drugs, especially amidopyrine, the barbiturates,²⁸ or their many combinations and, more recently, sulfanilamide, is important.

It is a common observation that there is a failure of bone marrow in certain virulent or overwhelming infections, but such a failure should be recognized as part of the clinical picture resulting from widespread sepsis and not as a selective granulocytopenic episode. It is known that the toxins of some organisms do depress granulopoiesis, and there may be occasional cases in which true secondary agranulocytosis develops on this basis.

In all other cases, however, definite neutropenia is present, often for days, before infection makes its appearance. This has been repeatedly shown in carefully followed cases in which a recurrence has developed.

There seems to be marked uniformity in the clinical course in these cases if a careful history is obtained. For a variable period of hours or days there are prodromal symptoms of fatigue and lassitude, slight chilliness, and headache. There may be repeated similar episodes over a relatively long period in the case of a chronic neutropenic individual before a severe attack occurs, but in the fulminating case, there may be only a few hours of such malaise. This condition is climaxed by sudden prostration, headache, soreness, and tenderness of the muscles of the neck (especially the sternomastoids), chills and fever, lethargy, or even coma. The necrotizing lesions which then appear may give rise to regional adenopathy. There is, of course, no pus or abscess formation, since there are no granulocytes, but ulceration and gangrene with sloughing or formation of membrane occur, especially in the mouth and pharynx or about the anus, rectum, and vagina. The skin may be involved as well as the gastro-intestinal tract or other systems.

The diagnosis is primarily dependent upon a leukocyte count of from 250 to 2,500 cells per cubic millimeter and a marked reduction or complete absence of granulocytes. The erythrocyte count is practically always above 3,500,000 and in uncomplicated cases the platelets are normal. Differentiation must be made primarily from acute leukopenic leukemia and from aplastic anemia.

Good nursing, hygienic care of lesions, and protection from new infections are the important features of treatment. Removal of all drugs to which the attack may be secondary is necessary. Transfusions are almost universally resorted to in aiding bodily defense, but there is some evidence that this procedure may retard the bone marrow response by artificially meeting the demands thrown upon it. One-twentieth erythema doses of roentgen rays over the bones for a stimulating effect have not been successful and most authors are of the opinion that such doses are depressing or destructive. Liver extract has been used with variable reports of success or failure; it

evidently lacks the specific effect on granulopoiesis that it has on erythropoiesis.

Of the specific stimulants to granulopoiesis there are two which have both clinical success and experimental results to warrant their use, namely, pentnucleotide and yellow bone marrow. Jackson and Parker claimed to have reduced the mortality in this disease with pentnucleotide and advocate its administration in the average case as follows: 10 c.c. is given intramuscularly two or three times a day until the leukocyte count definitely rises and young neutrophils appear; 10 c.c. is then given daily until the leukocyte count has been normal for several days. In extremely severe cases especially with a leukocyte count below 1,000 per cubic millimeter, larger doses of 40 or 50 c.c. are given daily; part of this may be administered intravenously by means of the slow drip method, using a dilution of 20 c.c. of pentnucleotide in 1,000 c.c. of physiologic saline solution. Jackson and Parker warned against giving this drug in cases in which there was a history of possible anaphylaxis or in the presence of severe cardiac damage. Most patients complain of considerable pain at the site of injection, and this is the greatest objection to the treatment.

Two of us^{8,31} have used yellow bone marrow extract with very gratifying results, having obtained a favorable clinical and hematologic response in all cases in which adequate amounts could be given and in which hopeless complications were absent. The preparation used was a concentrate prepared from the yellow marrow of cattle. It is supplied in $3\frac{1}{2}$ -grain (0.22 gm.) capsules for oral administration and 50 to 200 capsules are given daily until a response is evidenced by monocytosis followed by the appearance of young granulocytes. The dose is then reduced to 25 capsules a day until the leukocyte count is normal. After the count is at a normal level, 10 capsules a day are given as a maintenance dose for several weeks.

Not infrequently patients are seen for the first time in the late stages of the disease, when ulceration and necrosis of the pharyngeal mucous membrane may be so severe that swallowing is extremely painful. The difficulty of administering bone marrow extract in capsule form to these patients is obvious.

In such cases a nasal catheter should be passed into the stomach and the extract administered through it in liquid form. In order to obtain a liquid form of the extract, the proper number of capsules should be heated in a water bath until they dissolve. Fragments of capsules which do not dissolve should be forced through the catheter with a syringe. Large doses of the extract may be given in this way, the catheter being left in place until granulopoiesis is well under way and the lesions in the throat are beginning to heal. Nourishment may also be given through the catheter.

Recently, Marberg and Wiles made a preliminary report on twenty patients who were treated with their concentrated yellow bone marrow extract which was dissolved in a bland oil for oral administration. In only fourteen cases was a satisfactory diagnosis of granulocytopenia made and of the fourteen patients, only one showed an unsatisfactory response; in this case the condition was complicated by diabetes and appendicitis.

From this it is evident that granulocytopenia is not as hopeless a condition as was formerly believed and that some progress has been made in developing a specific type of treatment. It must be stressed, however, that early diagnosis with prompt institution of treatment probably means the difference between success and failure in the handling of these cases.

HEMORRHAGIC PURPURA

This disease gives rise to hematologic emergencies by hemorrhage, which in turn is dependent chiefly upon an inadequate number of blood platelets for proper clot formation. A paucity of platelets in the peripheral blood may be secondary to infection, toxins, drugs, or other agents, or it may be primary or idiopathic. Current medical opinion regarding the pathologic physiology of primary thrombocytopenic purpura is divided; many authorities credit the bone marrow with normal platelet production and incriminate the spleen as a selective destructive organ, whereas others believe that platelet production is depressed in the bone marrow, probably by splenic influence. In this connection recent observations by Troland and Lee are apparently important.

Hemorrhagic purpura is primarily a disease of exacerbations and remissions, and even very severe acute cases may suddenly go into a spontaneous remission; conversely, the mildest chronic type may have severe hemorrhagic episodes demanding emergency treatment. Hemorrhage may vary from scattered petechiae in the relatively benign, chronic case to the acute case with severe exsanguinating hemorrhage from any part of the body. Cerebral hemorrhage is often terminal and its appearance is always ominous.

The hematologic findings, in addition to the evidence of hemorrhage and capillary permeability, are prolonged bleeding time, normal coagulation time, prolonged or absent retraction of clot, and decreased or absent platelets on repeated counts. In addition, there is evidence of an active bone marrow with polychromatophilia and anisocytosis, especially if hemorrhage has been at all prominent; unless there is a leukemoid reaction accompanying a massive loss of blood, there should be little or no immaturity of the leukocytes. The spleen may or may not be palpable.

This condition must be primarily differentiated from hemophilia, acute or leukopenic leukemia, and from aplastic anemia. Purpura fulminans, bacterial endocarditis, allergic purpura, and scurvy must also be considered. Most confusing are the little understood "familial bleeders" who have normal platelet counts but a prolonged bleeding time or who have normal platelets and prolonged or absent clot retraction. Very careful study should precede the acceptance of a diagnosis of essential thrombocytopenic purpura since splenectomy, which is usually beneficial in this condition, may precipitate a rapidly fatal reaction if the case is one of leukemia.

Treatment may be medical, or medical and surgical, each case demanding individualization of treatment based upon the response and the immediate needs. In spite of the availability of splenectomy and its reputed success in the management of the disease, experience has shown it not to be universally applicable or completely successful. It has been found that patients in severe exacerbations of chronic purpura who do not respond to medical management seldom do well following splenectomy.

The prognostic moccasin venom reaction of Peck and his

coworkers promises to be of great aid in gauging the response to medical treatment. Repeated use of this test allows one to gauge the effect of medical management, and a changing reaction to venom which precedes clinical changes in the patient gives the physician a chance to anticipate therapeutic needs. Clinical findings of lessened hemorrhage, increasing blood count, increasing evidence of bone marrow activity in the blood smears, and symptomatic improvement should also guide therapy.

Transfusion is the most beneficial aid in medical treatment, both in replacing lost blood to correct the anemia and in aiding proper clot formation. It should be repeated without hesitation as frequently as necessary. The use of citrated blood is effective.

The efficacy of moccasin venom has not yet been clearly demonstrated in the treatment of hemorrhagic purpura; results have been discussed by Peck and his coworkers.

One of us⁶ had classified cases of thrombocytopenic purpura as incipient and recurrent and has discussed the indications for therapy in the acute phases of each type. The recurrent type seen in acute exacerbation is most hazardous, and during an exacerbation, every opportunity should be given by medical treatment to induce some indication of remission before splenectomy. If the response to medical treatment is not satisfactory, the hope of beneficial results from splenectomy is not great. The postoperative course of such patients is usually stormy and the mortality high. If, however, the response to medical treatment is good, splenectomy should not be delayed too long as cerebral hemorrhage may intervene.

HEMOPHILIA

Hemophilia is usually readily diagnosed by the characteristic family history of hemorrhagic tendency confined to the male, and transmitted by the female members of the family; evidence or a history of frequent joint hemorrhages; and prolonged hemorrhage from minor lacerations or following extraction of teeth. The laboratory data are quite characteristic and, with the history and physical findings, differentiate this hemorrhagic diathesis from other blood dyscrasias associated

with abnormal bleeding. The most characteristic finding is prolongation of the clotting time of the venous blood; the prothrombin time is abnormally lengthened, whereas the thrombocyte level is normal; the bleeding time is normal or only slightly prolonged, and the clot retracts if a clot eventually forms. Morphologically, there are no significant changes in the peripheral blood.

Reports have appeared in the literature of cases quite similar to, if not identical with, hemophilia which affected females. There is usually a familial tendency toward hemorrhage and the laboratory findings are those associated with true hemophilia, although occasionally there is some decrease in thrombocytes. In most of these cases there has been no evidence of male hemophilia. Most authors regard this condition as female hemophilia but do not feel that it is the same disease as male hemophilia.

Pseudohemophilia has been recognized for many years and recently has been seen with increasing frequency. Fowler reported two such cases. The features are recurrent hemorrhages from the mucous membranes, uterus, or gastro-intestinal tract. Hemorrhage may be mild or severe and occasionally may prove fatal, but it usually is less severe with advancing age. Manifestations may appear in infancy or be present at birth but they usually appear in childhood or adolescence. Purpura is uncommon. The laboratory findings are prolonged bleeding time, normal coagulation time, normal or high thrombocyte count. The prothrombin time and clot retraction time are usually normal but they may be prolonged and may vary considerably in the same patient from time to time. Both males and females are affected and the condition may be transmitted by either sex directly to sons and daughters. It is probable that many cases are grouped under this heading which, with future research and greater understanding of details of the mechanism of blood coagulation, can be more definitely placed under specific types of blood dyscrasias.

The treatment of hemophilia is often most discouraging. At present, transfusion offers the most encouragement and is indicated in all cases of serious or moderately serious hemorrhage. Much controversy has arisen with regard to the superiority of direct transfusion of whole blood over citrated blood.

At present it is the consensus that they are equally efficacious in the control of hemorrhage. Coagulating snake venom (either that of the fer-de-lance or of Russell's viper) for local application is of some value in the control of localized hemorrhage, particularly after extraction of a tooth, or when the venom may be applied directly to the bleeding lesion. MacFarlane has found a 1:10,000 solution of Russell's viper venom has a remarkable hemostatic effect when applied directly to the tooth socket or external wounds of patients with hemophilia.

In 1936, Timperley, Naish, and Clark, by the use of an extract of egg white, were able to reduce the coagulation time and control hemorrhage in hemophilia when the material was given intramuscularly or intravenously. This substance is not claimed as a cure for hemophilia for it merely controls hemorrhage, and to do this adequately repeated injections are necessary.

Another preparation, known as "Sango-stop" and consisting principally of pectin, has been used with some success in the control of hemorrhage by Gohrbrandt. The material is given intramuscularly. In our experience with two cases of hemophilia, in an acute exacerbation this material had no apparent effect in controlling hemorrhage.

Patek and Taylor observed that cell-free normal plasma contained a substance which shortened the coagulation time of the blood in hemophilia. In further studies they have precipitated a globulin from normal plasma which, when suspended in saline solution, was as effective as whole plasma in reducing the coagulation time. This same effect could not be obtained by the equivalent material from hemophiliac plasma.

The use of various ovarian substances has not yet proved of clinical value although much investigative work has been and is still being carried out along this line. There is, however, evidence that a placental extract may produce a reduction in the coagulation time. It is probable that in the near future some of these substances will become available but, at present, the most satisfactory and generally obtainable treatment is coagulating fer-de-lance venom for local application and repeated transfusions of blood.

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THE DIAGNOSIS AND TREATMENT OF EXTRACARDIAC VASCULAR EMERGENCIES

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SUDDEN interruption of the circulation to a vital organ or extremity or the rupture of a blood vessel are common catastrophes in middle life. Such an incident should be considered as an emergency in every case and proper treatment should be instituted without delay. Sudden occlusion of a blood vessel is usually due to obstruction from a thrombus or from the lodgment of an embolus from a distant source.

Thrombosis which produces sudden occlusion almost always occurs in an artery previously affected by arteriosclerosis or aneurysm, or by an inflammatory process, usually thromboangiitis obliterans. Only rarely does extension of an inflammatory process or tumor into the artery, increased coagulability of the blood, or local trauma to the wall of the vessel cause thrombosis.

Emboli which cause sudden arterial occlusion come from areas of thrombosis on the wall or valves of a diseased heart or aorta. The exception is a pulmonary embolus which usually comes from a thrombus in a vein affected with thrombophlebitis.

Nontraumatic rupture of an artery with hemorrhage results from weakening of the arterial wall through arteriosclerotic changes or aneurysm formation. The cerebral arteries are frequently the site of such a rupture, and in such cases intra-arterial hypertension is an important contributing factor.

Massive venous occlusion commonly occurs after major surgical procedures and in association with various infectious diseases and conditions. The thrombus may result from inflammation or injury of the wall of a vein, stasis of the circulating blood, or disturbances in coagulation of the blood.

There is no general agreement as to which of these factors plays the major rôle in postoperative thrombophlebitis.

The extracardiac vascular emergencies usually encountered are cerebral hemorrhage or thrombosis, pulmonary embolism, mesenteric vascular occlusion, peripheral arterial occlusion, and acute thrombophlebitis. Although in many cases death occurs before much can be done to aid the patient, a fatalistic attitude is not justifiable. Even in the more serious cases, a life or an extremity can be saved by instituting proper treatment without delay.

CEREBRAL HEMORRHAGE OR THROMBOSIS

Symptoms and Physical Signs.—Premonitory symptoms, such as transient vertigo, headaches, retinal hemorrhages and epistaxis, precede the majority of major cerebrovascular accidents. In some cases these symptoms are the result of vascular accidents of a minor nature or of cerebrovasospastic crises. However, the onset may come without warning. The victim, while engaged in some relatively strenuous activity, suddenly falls and becomes unconscious. There is a minimum of shock; the breathing becomes stertorous and labored and the pulse is forceful and bounding. Inasmuch as hypertension is an important etiologic factor in 95 per cent of the cases of cerebral hemorrhage, the blood pressure will usually be found to be elevated, often to very high levels.

Examination will reveal hemiplegia involving the face, tongue, arm and leg. The pupils may be dilated and the pupillary reflexes and corneal reflexes absent or diminished; if conjugate deviation of the eyes is present, the eyes look toward the site of the lesion. Incontinence of urine and feces may occur.

If the hemorrhage is extensive or near the vital centers, death may ensue within a few minutes. Usually, consciousness is regained after a few hours and a residual hemiplegia is evident. As consciousness is regained, the reflexes return and muscle tonus is increased, resulting in a spastic hemiplegia.

Diagnosis.—The differential diagnosis of cerebral vascular accident and other conditions of coma is not, as a rule, difficult. A history of one or more of the various premonitory symptoms or of a previous cerebrovascular accident or hypertension

should lead one to think first of a vascular cause of the coma. Ordinary syncope, epilepsy and hysteria can be excluded by the absence of such neurologic signs as abolished pupillary and corneal reflexes and the shorter duration of the coma, especially in cases of syncope and epilepsy. Uremic and diabetic coma can be excluded by an examination of the blood and urine, although small quantities of sugar may be found in the urine following a cerebral hemorrhage. The age of the patient and the unilateral neurologic manifestations will be particularly helpful in differentiating the attack from diabetic coma.

The differentiation of cerebral hemorrhage from cerebral thrombosis is not so readily accomplished. A slower onset of symptoms, frequently while the patient is not active, and the absence of signs of hypertensive disease indicate thrombosis rather than hemorrhage.

Treatment.—When a cerebral hemorrhage is impending or has occurred, the patient should be placed in bed and kept absolutely quiet in a darkened room. If he appears plethoric and his blood pressure is extremely high, bleeding of from 300 to 500 c.c. of blood is advisable. Sedatives should be given by rectum, preferably sodium amytal, grains 3 (0.2 gm.) to grains 6 (0.4 gm.) to allay restlessness. No attempt should be made to feed the patient or even to give fluids by mouth until it is certain that he can swallow. Ice caps should be used with caution, if at all, because of the tendency of cold applications to elevate the blood pressure. A hypertonic solution of d-glucose (250 c.c. of a 20 per cent solution) may be administered intravenously with benefit. Drainage of spinal fluid should be instituted if unconsciousness persists and if there is evidence of increasing intracranial pressure. Surgical intervention is almost never advisable.

PULMONARY EMBOLISM

Symptoms and Physical Signs.—The initial symptom of a large pulmonary embolus is pain in the chest which is projected laterally and which is often aggravated by inspiration. Such pain is usually followed by or associated with marked dyspnea and cyanosis. Dyspnea and cyanosis, however, may be minimal or absent and the picture may be mainly one of

shock, with pallor, sweating, tachycardia, and a marked drop in blood pressure. A pleural friction rub is often heard in those cases in which infarction occurs rapidly.

Objective findings of pulmonary and pleural involvement, particularly a pleural friction rub and signs of consolidation, may not become evident until several hours have elapsed. Signs of failure of the right side of the heart, such as marked accentuation of the second pulmonic sound, a loud murmur over the pulmonic area and distention of the veins of the neck, may cause one to locate the lesion in the heart.

Roentgenologic examination of the thorax is usually an aid in early diagnosis, although in many cases no changes suggestive of pulmonary embolism will be noted.

Massive pulmonary embolism is often preceded by lesser embolic episodes which have not been recognized. It is extremely important to evaluate properly these early embolic episodes as much can be done to prevent the subsequent occurrence of massive embolism.

Diagnosis.—On perusal of the symptoms of pulmonary embolism it will be evident that some of them occur also in acute coronary thrombosis. According to Barnes, the symptoms common to both conditions are sudden onset, vomiting and collapse, marked fall in blood pressure, tachycardia, leukocytosis and elevation of temperature. In some cases, a differential diagnosis between the two conditions is impossible in the early stages. Previous attacks of angina pectoris should be considered as important evidence supporting the diagnosis of acute coronary thrombosis. The pain of coronary occlusion is usually more centrally located in the thorax than is that of pulmonary embolism. Cyanosis and marked dyspnea are more characteristic of pulmonary embolism than of acute coronary occlusion.

The electrocardiogram is of great aid in the differential diagnosis of pulmonary embolism and coronary occlusion. Since the characteristic electrocardiographic findings in pulmonary embolism have been established by Barnes and by McGinn and White, a correct diagnosis now can be made in many cases when it previously would have been impossible. These characteristic electrocardiographic changes, however, are not present in all cases of pulmonary embolism. In cases

of acute infarction of the posterior basal portion of the left ventricle the electrocardiographic changes are more like those of pulmonary embolism. Table 1, which was compiled by

TABLE 1

ELECTROCARDIOGRAPHIC DIFFERENCES BETWEEN ACUTE PULMONARY EMBOLISM AND ONE TYPE OF ACUTE CARDIAC INFARCTION

	Acute pulmonary embolism.		Acute infarction of the posterior portion of the left ventricle.
S_1	Constantly present and usually prominent	S_1	Absent, or if present not exaggerated.
$S-T_2$	Take off usually below zero level	$R-T_2$	Usually elevated; rarely isoelectric and never depressed
T_2	Diphasic, monophasic, or upright; rarely inverted	T_2	Usually inverted
$R-T_3$	Occasionally slightly elevated	$R-T_3$	Greatly elevated as a rule
T_3	Inverted; may be cove plane	T_3	Usually inverted
Q_3	Frequently fairly prominent; Q_3 pattern not present	Q_3	Frequently markedly prominent; Q_3 pattern commonly present
Q_4	Usually within normal limits	Q_4	Usually within normal limits
T_4	Usually upright; may be flat or diphasic	T_4	Usually inverted

Barnes, shows the characteristic electrocardiographic findings in cases of acute pulmonary embolism and a comparison with the findings in cases of acute infarction of the posterior portion of the left ventricle.

Treatment.—When massive pulmonary embolism has occurred, treatment may be of little avail as many of the patients die in spite of any measure which can be carried out. The patient should be placed in a semi-upright position and fresh air or oxygen should be made available. If cyanosis is marked, oxygen therapy should be instituted at once. Morphine should be given to control pain and restlessness. One-half grain (0.032 gm.) of papaverine hydrochloride should be given intravenously when available. Venesection may be of value in those cases in which signs of right heart failure are prominent.

Surgical removal of the embolus may be considered in desperate cases when a set-up is available for carrying out the Trendelenburg operation.

MESENTERIC VASCULAR OCCLUSION

Mesenteric vascular occlusion is one of the most serious of all vascular accidents. The occlusion involves the superior mesenteric vessels in almost every case; consequently, the circulation of a large portion of the bowel is interfered with and extensive infarction and gangrene occur.

In Larson's series of cases, the mesenteric artery or vein was the site of occlusion in about an equal number of cases. In approximately 15 per cent of his cases both the artery and vein were involved in the occlusive process. When this occurs, the course of the illness is more severe and fulminating.

Symptoms and Physical Signs.—The onset of symptoms is usually sudden, simulating other acute abdominal conditions. Whether the occlusion occurs in the artery or vein, the symptoms and physical signs are essentially the same, although if the vein alone is involved, the symptoms may be less acute.

The initial symptom is severe pain which at first is colicky and generalized over the entire abdomen. Nausea and vomiting occur shortly after the onset but may subside in a few hours. Diarrhea and melena are the most characteristic early symptoms. Shock is often profound and the condition of the patient sometimes rapidly becomes critical.

Physical examination of the abdomen will reveal only moderate tenderness and little or no muscular rigidity or spasm. As the condition progresses, fever, leukocytosis, abdominal distention, and finally signs of ileus and peritonitis, will be observed.

Diagnosis.—The differentiation of mesenteric vascular occlusion and other acute abdominal conditions, particularly other forms of intestinal obstruction, may be exceedingly difficult. The absence of marked muscular rigidity or spasm until some time has elapsed may be helpful in ruling out an acute inflammatory condition in the abdomen or of a perforated viscus. The salient points in the diagnosis of mesenteric vascular occlusion, as laid down by Kussmaul and Gerhardt, will be found of great value in arriving at a correct

diagnosis. They are: (1) a source of an embolus; (2) melena, not explained by a primary intestinal lesion; (3) rapid and excessive fall in temperature; (4) severe, colicky abdominal pain; (5) embolic or thrombotic phenomena elsewhere in the body, and (6) later, distention of the abdomen and evidence of intra-abdominal fluid. In most cases the differential diagnosis is not of great practical importance as surgical exploration will usually be carried out.

Treatment.—The treatment is surgical.

SUDDEN PERIPHERAL ARTERIAL OCCLUSION

Symptoms and Physical Signs.—Occlusion of a peripheral artery may occur from thrombosis, usually in a previously diseased artery, or as the result of the lodgment of an embolus from a distant source. In either case the symptoms are essentially the same. The initial symptom is usually pain in the affected extremity which may or may not be near the site of obstruction. It is important to realize, however, that sudden occlusion may occur with little or no pain at the onset. In some cases the first symptoms will be numbness or coldness in the extremity or mild paresthesias. In rare instances, pallor and coldness first call the patient's attention to the extremity. Any of these symptoms may develop acutely, although in more than half the cases in the series reported by McKechnie and Allen the symptoms developed gradually over a period of from one to several hours. There is rarely any shock, such as is common in cases of coronary occlusion or pulmonary embolism. The occurrence of these symptoms should incite suspicion of a possible acute arterial occlusion, and inspection of the extremity should be carried out at once. Usually the diagnosis is evident, as the limb appears ischemic and the skin is cold. The reflexes may be absent or diminished and sensation and muscle strength may be impaired. Pulsations in some or all of the palpable arteries of the extremity will be absent. The site of the absent pulsations is determined by the location of the occlusion, although if there is much arterial spasm, pulsations may be temporarily absent for some distance above the actual site of occlusion.

Diagnosis.—The diagnosis of acute arterial occlusion is easy if the possible significance of the symptoms described is

borne in mind and a careful examination of the extremity is made.

Acute thrombophlebitis must be differentiated from acute arterial occlusion because of the radically different methods of treating the two conditions. The main points in the differential diagnosis are given in table 2. Usually the normal tem-

TABLE 2
DIFFERENTIAL DIAGNOSIS OF ACUTE ARTERIAL AND ACUTE VENOUS
OCCLUSION OF EXTREMITIES

Physical signs.	Acute arterial occlusion.	Acute venous occlusion.
Color.....	White at first; later mottled	Diffusely cyanotic
Size.....	Shrunk	Swollen or edematous
Skin temperature.....	Reduced	Normal
Superficial veins.....	Collapsed	Distended
Postural color change.	Marked pallor on elevation; slow return of color on de- pendency	Less than normal pallor on elevation; increased cy- anosis on dependency
Sensation.....	May be impaired	Normal
Muscular power.....	May be decreased or absent	Normal
Arterial pulsations....	Absent	Usually present

perature, distended veins, edema and normally pulsating arteries easily distinguish the extremity affected by thrombophlebitis from the ischemic extremity in cases of sudden arterial occlusion. If reflex arterial spasm is present and pulsations are absent in some of the arteries, it may be necessary to wait until several hours have elapsed before a definite diagnosis can be made. If there is any serious question as to the diagnosis, it is better to treat the condition as one of arterial occlusion, as little damage could be done if it should turn out to be thrombophlebitis, whereas on the other hand much damage might be done by treating an extremity affected by arterial occlusion by the methods generally used in treating thrombophlebitis.

Treatment.—In no instance is a favorable outcome more dependent on the quickness of instituting proper treatment

than in acute arterial occlusion. Any unnecessary delay endangers the chances of recovery of the extremity. The patient should be in bed at complete rest, and great care should be taken to avoid injuring the ischemic tissues. It should be well known that tissues with a decreased blood supply do not tolerate heat well; heat should therefore never be applied directly to the skin of the extremity. The extremity should be wrapped in several layers of cotton material to conserve its intrinsic heat. A heat lamp or baker in which the heat is carefully regulated may be useful in increasing warmth. The head of the bed should be elevated and the extremity placed in a dependent position in order to use the effects of gravity in increasing circulation. Morphine or codeine must be given if needed to control pain. Papaverine hydrochloride will often produce satisfactory vasodilation if given intravenously, beginning with a dose of $\frac{1}{4}$ grain (0.016 gm.). Double this amount may be given in thirty minutes if vasodilation has not occurred and there is no unfavorable general reaction from the first dose. The initial dose can be repeated every four to six hours when there is evidence of further failure of circulation. If large amounts of morphine or codeine have been given, the respiration should be watched carefully before giving repeated doses of papaverine, as some depression of the respiratory centers can occur. Theobromine, in doses of 20 grains (1.3 gm.), may be given by mouth, although its vasodilating effect is probably too feeble to be of much value in cases of acute occlusion. Ethyl alcohol, administered orally in water or fruit juices, will produce marked vasodilation in many cases; about 0.5 c.c. of ethyl alcohol for each kilogram of body weight is an effective dose. This may be repeated three or four times during twenty-four hours. Treatment by alternating positive and negative pressure (pavex method) may be used if a machine is available. However, I have not found that this method of treatment is strikingly more effective than other methods which I have already outlined. Certainly it is not justifiable to use the pavex method in these cases to the exclusion of all other forms of treatment.

If these measures do not result in improvement of the circulation within a short while, surgical removal of the clot should be considered when the occlusion is due to an embolus.

If proper medical treatment is instituted early, operation will rarely be necessary; if instituted late, operation will be of no more avail than any other method of treatment.

ACUTE THROMBOPHLEBITIS

Symptoms and Physical Signs.—The symptoms and findings in the acute stage of thrombophlebitis vary with the location of the thrombosis. If a large vein (like the femoral, iliac, or axillary) is involved, the initial symptom will usually be pain over the area of the inflamed vein. This is followed, after a variable period of time, by congestion of the extremity, distention of the superficial veins, and edema, although the last named is often delayed and may not become evident until the patient gets out of bed and allows the extremity to remain in a dependent position. Some fever is present at the onset in the majority of cases; in Barker's series of cases the temperature was rarely above 101° F.

Diagnosis.—The diagnosis is not difficult if the nature of the lesion is remembered and signs of venous obstruction are looked for. In the first few hours thrombophlebitis may be confused with sudden arterial occlusion. Any real difficulty in differentiating the two conditions should rarely be met with as the signs of arterial occlusion are quite different from those of venous occlusion (table 2).

Treatment.—The treatment of thrombophlebitis is simple. If the phlebitis is localized in a superficial vein, rest in bed is not so urgent, although excessive activity should be avoided. Rest in bed is imperative, however, if one of the larger veins is involved. The leg should be elevated to an angle of 30 degrees and heat, preferably in the form of hot, wet packs, should be applied to the entire extremity. Care must be taken not to burn the skin from excessive heat. Pain usually is relieved by hot applications, although in the case of hypersensitive persons or when there is much perivenous reaction, anodynes or even opiates may be needed to control it.

When the temperature has been normal for a week and local tenderness and edema have subsided, the patient may be allowed to get up. An adequate bandage or stocking should be applied to the extremity.

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RENAL EMERGENCIES

MELVIN W. BINGER

IN the course of medical practice physicians are confronted frequently by various types of acute renal complications that require careful differentiation and prompt, specific treatment. When faced with such a problem, naturally the questions arise regarding the nature of the underlying pathology, ways of distinguishing between the various disease entities which may be present and how to proceed with a rational therapeutic regimen.

To discuss the problem of renal emergencies in a single communication naturally demands brevity and necessitates elimination of many fine points in technic, diagnosis and treatment from consideration; the reader's familiarity with these must be assumed. Renal emergencies arise often without warning in surgical as well as in nonsurgical cases and it is a credit, indeed, to the surgeon or internist if he is wholly familiar with this complex problem. In this discussion, it is difficult to indicate under what conditions an emergency may be said to have ended and routine treatment to have been instituted.

POSTOPERATIVE ANURIA

It is provoking, to say the least, to observe, a few days after an extensive operative procedure has been performed, that the output of urine has decreased to almost nothing, that the urine contains large amounts of albumin, casts, and blood and that edema and blood urea are on the increase. Naturally, the situation becomes desperate, calling for prompt, careful management.

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Often, a trace of albumin in the urine has been noted pre-operatively. A history of edema of the legs associated with albuminuria may have been obtained, or, at some previous

time, the specific gravity of the urine may have been low, around 1.010 to 1.015 and a few casts and erythrocytes may have been found in the urine. Often the patient states that the blood pressure had been found somewhat elevated and some degree of anemia had been present, all suggesting the possibility that, previously, mild chronic nephritis had existed. Closer questioning may reveal that the patient had scarlet fever in childhood, septic tonsils, or other infectious processes; or that he had frank edema associated with albuminuria. Among women, a history of toxemia of pregnancy often is obtained. Hypertension associated with secondary cardiac and renal involvement, chronic pyelonephritis, including tuberculosis of the kidney, renal stone, hydronephrosis, gout and polycystic kidney, all must be considered as underlying basic conditions. Acute suppression of urine that occurs following operation should suggest the possibility of some previous damage to the kidneys or vascular system. Acute toxic processes that occur postoperatively may be important contributing factors. The more common of these are bronchopneumonia, peritonitis, septicemia, infection of wounds, and absorption of toxic substances frequently associated with conditions such as malignancy of the stomach or bowel, and ulcerative colitis.

However, with oliguria usually there is associated a loss of appetite or anorexia and vomiting. The patient is listless and does not feel as well as usual. It is always advisable to catheterize these patients, even if they do not complain of difficulty in voiding or of distress associated with the bladder. I have seen patients unable to void more than 100 to 200 c.c. of urine a day, for a day or so, postoperatively, who were thought to have some intrinsic renal or cardiac lesion. Instead, they had a residual urine of 1,000 c.c. or more, and regular catheterization or insertion of a retention catheter remedied the situation. Urinalysis and examination for albumin, sugar, blood, casts, and pus should be made. If the patient has a fever a centrifuged specimen of urine should be examined for organisms and cultured.

Estimations of the blood urea and of the carbon dioxide combining power and chlorides of the plasma are advisable. If there is much albumin in the urine, the serum protein and, if possible, the albumin-globulin ratio should be estimated.

A more accurate but more complicated test is estimation of the colloidal osmotic pressure. If there is much fever, the blood should be cultured, the number of leukocytes and the sedimentation rate should be determined. Obviously, the extent of these tests depends on the situation at hand and on the difficulty of the problem; by no means should they be considered and employed as routine procedures. They are useful diagnostic instruments that should be used when necessary.

Correct interpretation of the laboratory and clinical findings is very important. Obviously, the primary objectives are to reestablish if possible the normal output of urine and to rid the body of the accumulating soluble waste products of metabolism and of excess fluid, if edema is present.

A safe and usually very effective initial procedure is intravenous administration of a concentrated solution of d-glucose together with 10 c.c. of aminophyllin. Two hundred to 500 c.c. of a solution of 20 per cent d-glucose can be given at one time.* The diet should be one low in content of salt and condiments; moderate restriction of the intake of protein to 50 gm. a day should be enforced. If there is much edema the fluid taken by mouth should be limited to 1,000 c.c. a day until a negative water balance is attained, at which time intake of fluid can be increased. It is inadvisable to push intake of fluid to excessive amounts if this fluid continues to accumulate in the tissues of the body and in the large cavities. By so doing the already impaired functions of the kidneys, heart, liver, and other organs are burdened further by the excess fluid.

If the patient is able to take medication by mouth, mild diuretics may be tried. Potassium nitrate usually is tolerated well. It can be obtained in enteric-coated pills of 0.5 gm. each, four to six of which can be given after meals. If the output of urine is 300 c.c. or more a day and if the blood urea is below 50 mg. per cent, 1 c.c. of salyrgan or other organic mercurial diuretic can be given intravenously. Provided that toxic effects such as diarrhea or bloody urine are not noted and that a diuretic response has occurred, 2 c.c. may be given the following day and 2 c.c. every third or fourth day thereafter, as long as such treatment is indicated. Salyrgan can be given very sat-

* Sucrose has been used in like amount and concentration with good diuretic response.

isfactorily with potassium nitrate. Ammonium chloride or ammonium nitrate may be given instead of potassium nitrate, but the ammonium salts are more toxic than the potassium salts, tend to produce acidosis and are not tolerated as well by the patient.

Should the serum protein be less than 4.5 or 5 gm. per cent (the critical level below which occurrence of edema is observed) it may be necessary, in addition to the above measures, to increase the colloidal osmotic pressure of the blood. This may be done by giving repeated transfusions of whole blood, or much more simply and economically, by giving a solution of acacia intravenously. Five hundred c.c. of a solution of 6 per cent acacia and 0.9 per cent sodium chloride may be given on either successive or alternate days for three or four administrations, giving the patient a total of 90 to 120 gm. of acacia. If the underlying condition is nephrosis associated with a low colloidal osmotic pressure of the blood, usually a distinct diuretic response will be obtained. In cases of low serum protein, it is well to increase the protein intake to 75 or 100 gm. a day.

In the event that myocardial failure is a factor in suppressing the excretion of urine and in producing edema, naturally, steps should be taken to increase cardiac efficiency. Space does not permit me to consider in detail the differential diagnosis of various cardiac conditions that may arise postoperatively causing suppression of the excretion of urine with resultant edema. Such a condition might be mistaken easily for primary renal disease. However, if the situation is introduced by dyspnea, pain in the thorax, râles in the lungs, increasingly irregular pulse and cyanosis, acute myocardial failure should be suspected and, if possible, the underlying lesion that is producing the situation should be ascertained. It should be determined whether or not hypertension exists or has existed. The possibility of coronary thrombosis must always be kept in mind, especially when dealing with patients past middle age, if evidence points to myocardial disease. Auricular fibrillation and acute pericarditis are to be considered. Careful physical examination of the heart and lungs, roentgenologic examination of the thorax and electrocardiographic examination are valuable aids to diagnosis. In most cases, digitalis can be

given by intramuscular or by oral administration and the patient can be digitalized in the usual manner. Administration of concentrated d-glucose is advisable and in amount and concentration similar to those used in treatment of acute primary renal failure. Organic mercurial diuretics such as salyrgan, novasurol, or mercupurin can be given freely in treatment of cardiac complications, even though the blood urea may be elevated, since, as a rule, the renal substance is not primarily damaged, and elevation of the blood urea is usually the result of renal congestion. If, however, satisfactory diuresis is not obtained on initial injection of salyrgan, it is not advisable to continue its use, as, most likely, more harm than good will result. The diet should be light and easily digestible and the intake of fluid should be about 1,000 c.c. a day. The patient usually is more comfortable with the head of the bed elevated. If cyanosis is pronounced and the patient is dyspneic, oxygen can well be administered by means of an oxygen tent or by means of a nasal catheter, if a tent is not available. Venesection is advisable in some cases and removal of 200 to 600 c.c. of blood often assists the patient over a bad crisis.

NEPHRITIS

Occurrence of oliguria or anuria unassociated with operation takes on an aspect different from that of postoperative oliguria or anuria, but, none the less, it is a serious situation. It is always well to consider first the etiology of the condition. The age of the patient is important from the standpoint of etiology; also, the possibility of previous occurrence of infection should be considered. Among children and young adults and occasionally among older individuals nephritis may occur following acute infections, such as scarlet fever, acute tonsillitis, measles, pneumonia, mastoiditis, and so forth; it is well to obtain information regarding these in the history, if possible. The possibility of ingestion of poisonous substances such as corrosive sublimate must be considered. Among older individuals the possibility of vascular disease associated with hypertension, and of cardiac failure must be considered and conditions such as cirrhosis of the liver, polyserositis, malignancy, polycystic kidney and myxedema all must be kept in

mind. It is only when these diseases are considered and are ruled out definitely that one safely can assume that they do not exist. Many a mistaken diagnosis has been made and improper treatment instituted merely because a diagnosis was assumed and was not made. It is granted that, when a physician is faced with an acute crisis such as anuria and edema, he cannot spend several days performing multiple, intricate and time-consuming tests to establish a water-tight diagnosis. However, it is maintained that, by obtaining a thorough history and by careful physical examination, he can ascertain in what category the case falls and simple laboratory procedures such as urinalysis, determination of concentration of blood urea, and determination of the number of erythrocytes and leukocytes can be done immediately. If possible, more elaborate tests such as roentgenologic and electrocardiographic examinations, complete chemical analysis of the blood, tests for hepatic function, determination of the basal metabolic rate, and so forth can be done as indicated while the patient is under observation and while tentative treatment is administered.

If the patient proves to have acute glomerulonephritis, he should be put to bed and should be kept warm. Hot packs may be applied to the region overlying the kidneys but their therapeutic value is questionable. A diet containing 40 to 50 gm. of protein a day, low in content of salt and free of condiments should be administered. The amount of fluid allowed depends on the degree of edema present. If there is definite pitting edema, not more than 1,000 c.c. of fluid by mouth should be permitted. The objective is to try to increase renal output. Frequently, rest in bed and keeping the patient warm are sufficient. Intravenous administration of 200 to 500 c.c. of a solution of 20 per cent d-glucose is usually helpful in establishing diuresis. Addition of 10 c.c. of aminophyllin to the solution of d-glucose when given stimulates the kidneys; I never have seen any contraindication to its use.

It is well to have an estimation of the CO_2 combining power of the blood and, if the CO_2 combining power is 40 vols. per cent or lower, some alkali such as sodium bicarbonate should be given either by mouth or intravenously to restore the acid-base equilibrium to normal. It is a well-known fact that a

kidney will not function well if acidosis is marked or if alkalosis exists; also, the kidney functions better when the acid-base equilibrium has been restored to normal. If acidosis is present, 200 to 500 c.c. of a solution of 5 per cent sodium bicarbonate can be given intravenously with comparative safety and, usually, will increase the CO_2 combining power 10 to 20 vols. per cent. If necessary, its administration can be repeated once each day for two days. The concentration of sodium chloride of the blood should be redetermined, however, and if an increase is found, sodium salts should be given sparingly as, in excess, they will have a tendency to increase the edema.

Alkalosis associated with suppression of urinary function can occur easily in cases of nephritis, frequently complicated by the presence of peptic ulcer. In these instances, the patient usually gives the history of consuming large quantities of alkali such as sodium bicarbonate with gradual onset of giddiness, nausea, vomiting, distaste for milk, headaches, scanty urine, edema, and increasing uremia. The CO_2 combining power will be 70 per cent or more. Withdrawal of alkali, intravenous administration of 1,000 c.c. of a solution of 10 per cent d-glucose and 1 per cent sodium chloride will usually restore the normal acid-base equilibrium; increasing diuresis will deplete the edema and reduce the elevated concentration of blood urea. In occasional cases it may be necessary to give ammonium chloride or calcium chloride.

The problem of active diuretics always arises and use of organic mercurial diuretics such as salyrgan, novasurol and mercupurin always must be considered. They should be given sparingly, if at all, when the total blood urea is elevated to 50 mg. per cent or more, when there is any degree of blood in the urine, or when anuria exists. Once diuresis is established organic mercurial diuretics aid remarkably in increasing flow of urine, thus ridding the patient of pent-up fluid and waste products in the tissues. If the output of urine is around 500 to 1,000 c.c. a day, organic mercurial diuretics can be given with comparative safety in doses of 2 c.c. intravenously, even though the concentration of blood urea is somewhat elevated. The initial dose, however, should not be over 1 c.c. in order to determine whether or not the patient is sensitive to it.

This sensitivity would be apparent if diarrhea, dermatitis, urticarial reactions, or hematuria occurred.

Of the diuretic salts I prefer potassium nitrate; it is given in the form of enteric-coated pills of 0.5 gm. each, four to six pills three times a day after meals. It is less toxic than ammonium chloride or ammonium nitrate and, as far as has been observed, it does not produce acidosis or impair the function of the kidneys. It is well tolerated and no harmful effects ever have been noted from its use. It has been given successfully in cases of edema associated with a concentration of urea as high as 150 mg. per cent.

Should diuresis be induced successfully and should the edema be reduced, it is important to consider whether or not focal infection exists. It is my opinion that foci of infection, such as occur in teeth, tonsils, mastoids, sinuses, and so forth, should be eradicated as soon as the condition of the patient permits. Even if there is blood in the urine, or even if the blood urea is somewhat elevated, active foci of infection should be removed. An autogenous vaccine has been made from material obtained from infected tonsils or infected teeth and has been given to some patients with evidence of benefit.

NEPHROSIS

Acute and chronic nephrosis, commonly called "lipoid nephrosis" because of the associated high content of blood cholesterol, has attracted much attention in recent years. Whether such a disease really exists or is merely a form of glomerulonephritis is a question of academic interest. It is sufficient that this discussion recognize it as a renal disease that requires prompt and vigorous treatment. The onset and etiology are like that of acute nephritis. However, there is more edema than usually is seen in cases of nephritis and more albumin and casts, but erythrocytes never are observed in the urine. There may be double refractile lipoid bodies in the urine. Usually anemia is not present and studies of the blood reveal, in addition to the high content of cholesterol in the blood, a low content of protein in the serum and a disturbed or inverted albumin-globulin ratio. If studies are carried to a fine degree, a marked decrease in the colloidal osmotic pressure of the blood will be found. Undoubtedly, this is the

basis for the presence of edema. Whether there is an increased permeability of the capillary walls in addition to the low content of serum protein is difficult to say. There is no measurable impairment of renal function in these cases except that albumin and globulin appear in the urine. When the colloidal osmotic pressure of the blood has been reestablished there seems to be no impairment of the ability of the kidney to excrete water.

Rational therapeutics, therefore, suggests that every effort should be made to restore the colloidal osmotic pressure of the serum. Such efforts should include: (1) increase of the intake of protein to compensate sufficiently for the amount of albumin lost in the urine. This means employment of a diet high in content of protein, that is, 75 to 150 gm. of protein a day; (2) repeated use of transfusion which, however, is expensive and, to some degree, is hazardous and of only temporary value, and (3) increase of the colloidal osmotic pressure of the blood by physical means. At the present time, the simplest method is injection of solution of acacia intravenously. This solution consists of 6 per cent acacia and 0.9 per cent sodium chloride. Five hundred c.c. can be given every day or every other day for three or four injections until 90 to 120 gm. of acacia have been administered, or until an amount sufficient to raise the colloidal osmotic pressure of the blood as nearly as possible to normal has been given. That diuresis is produced by other undetermined factors besides the raising of the colloidal osmotic pressure of the serum has been suggested by recent observations.

In addition, fluids should be restricted to 1,000 c.c. a day and preferably a diet low in content of salt should be given. Almost any type of diuretic may be given freely with fairly good success. Potassium nitrate seems to be the preferable diuretic salt. It is dispensed in enteric-coated pills of 0.5 gm. each; four to six of these should be given three times a day after meals. Ammonium chloride or ammonium nitrate may be given in similar doses, if preferred. If salyrgan, novasurol, or mercupurin is used an initial dose of 1 c.c. should be given intravenously and, if toxic manifestations do not occur, 2 c.c. may be given later, if necessary. If organic mercurial diuretics are used, appearance of toxic manifestations such as diarrhea,

dermatitis, hematuria and mercurial gingivitis should be watched for. As in the treatment of glomerulonephritis, foci of infection should be looked for and removed if present. The sooner this is done the better. The patient should be warned against chilling, fatigue and catching cold. Use of cold vaccine is advisable. A diet high in content of vitamins reinforced by cod liver oil or halibut liver oil may be of benefit.

HEMATURIA

There is probably no condition that will bring a patient to a physician more quickly than gross hematuria and, although, as a rule, it does not mean that an emergency exists, potentially it is a serious condition and demands prompt investigation. Occasionally, bleeding from a lesion of the bladder with formation of clots in the bladder is sufficient to obstruct the flow of urine and cause further dilatation of the bladder which, in turn, produces more bleeding. In such critical situations, a large catheter should be inserted, the bladder drained as nearly empty as possible and the clots broken up and washed out by repeated irrigations with warm solutions of boric acid. A retention catheter should be inserted; usually, the lesion will cease to bleed. As soon as possible, cystoscopic examination of the urethra and bladder should be performed to determine the source of hemorrhage and, if possible, that region should be fulgurated. If the region is too large, or if it is not the type that responds to electrical coagulation, performance of resection of the lesion or the part of the bladder containing the lesion may be necessary. Tissue should always be obtained from such a lesion for microscopic study to determine whether it is malignant or benign. Also, examination and culture of the urine should be made to determine whether infection is present. It is always advisable to examine the kidneys, ureters and bladder roentgenologically and to estimate the concentration of blood urea of these patients as soon as possible. Many times the source of hemorrhage is in the urethra or prostate and these regions always should be examined carefully. As a rule, if such is the case, blood will exude from the urethra independent of urination. If examination of the bladder and urethra does not give evidence of hemorrhagic lesions, the ureteral orifices should be examined to determine whether or

not blood is coming from either or both ureters. It may be necessary to perform a ureteral catheterization, retrograde pyelography and intravenous urography to determine the situation and nature of the lesion. These procedures, naturally, should be conducted by a competent urologist because of the many difficulties from both a technical and an interpretive viewpoint that make the attempt hazardous for anyone not familiar with the field. There are many lesions of the upper part of the urinary tract that can produce both gross and microscopic hematuria; the more common of these are stones, nephritis, tuberculosis, pyelitis, pyelonephritis, hypertension, malignant and benign tumors, polycystic kidney, trauma, and a condition termed "essential hematuria," the etiology or pathology of which is little known. However, as these conditions, in themselves, are not emergencies, space does not permit discussion of their treatment. It is sufficient to say that hematuria, either gross or microscopic, should not be ignored and that, after immediate steps are taken to determine the source of hemorrhage, proper treatment should be instituted.

ACUTE RETENTION

Acute retention is often so sudden and vicious in its onset that it is not necessary to explain the trouble to the patient, his one care at this time being to empty the bladder. Men are more often afflicted with acute retention than women. Symptoms such as slowing of the stream, dribbling, frequency, increasing nocturia, and a stream of urine that lacks force may have been developing for some time, indicating obstruction to the urinary flow from the bladder; suddenly the patient finds himself unable to void. If this situation is confronted, it is best to attempt immediately to pass a sterile small rubber catheter, draining the bladder, thereby postponing investigation of the cause of the trouble until later. In the event that a rubber catheter cannot be passed a more rigid catheter should be employed cautiously, care being exercised not to force it through tissue foreign to the channel. If it is difficult to pass the rigid catheter, a small cystoscope should be passed to determine the course of the channel and the type of obstruction. Sometimes, after such an examination, by careful manipulation the catheter can be passed. If not, it would then be necessary

to perform suprapubic cystostomy inserting a retention catheter. The obstructing lesion is usually a benign or malignant hypertrophy of the prostate gland, or a urethral stricture formed as a result of a former urethritis. Later, the obstructing lesion may be removed surgically by the transurethral route, or, as occasionally may be necessary, suprapubically.

Occasionally intermittent retention of urine is encountered owing to a ball valve action of stones in the bladder. Many of these may be crushed within the bladder and removed in fragments. They form in the bladder because of some obstruction at its neck which secondarily causes retention of urine resulting in infection. The obstruction may be caused by a stricture, congenital narrowing of the urethra, or hypertrophy of the prostate gland. The obstructing lesion should be removed surgically or the stricture should be dilated gradually. This procedure should be followed by a course of treatment with urinary antiseptics to eradicate infection of the urinary tract. If infection of the urethra or bladder exists, local treatment by lavage and instillation of a mild, soothing antiseptic will be necessary. For lavage of the bladder, a solution of boric acid or a solution of potassium permanganate (1:8000) may be used. One ounce of an emulsion of 7 per cent silver iodide is satisfactory for purposes of instillation.

Sometimes, postoperatively, especially if spinal anesthesia is used, acute retention of urine may occur which may be misinterpreted as anuria. If a patient does not void within eight to twelve hours following an operative procedure, a sterile catheter should be passed. This treatment should be repeated every eight hours until the patient is able to void voluntarily. Provided that the difficulty persists for any length of time, it may be necessary to insert a catheter and to leave it in place for several days. After the patient begins to void voluntarily, the urine should be examined for pus and should be cultured. If any degree of urinary infection is present, urinary antiseptics such as mandelic acid or sulfanilamide should be administered (see section on pyelonephritis).

Lesions of the spinal cord involving the tracts innervating the urinary bladder may result in urinary retention. This condition, frequently termed "cord bladder," actually results in loss of expulsive force and ability to relax the urethral

sphincter. Usually, the condition begins gradually. There is increasing difficulty in voiding, with delay in starting the stream, which has become slow and weak. However, the patient frequently finds himself unable to void at all. As catheterization is necessary, it is advisable to teach the patient self-catheterization in order that he may take care of his needs at regular intervals. Should infection of the urinary tract develop, the modern urinary antiseptics may be given as in treatment of any bacilluria. Many patients who have lost control of the bladder altogether are obliged to wear a rubber urinal bag strapped to the leg. Such a contrivance causes little discomfort and, as a rule, patients do not mind the inconvenience.

In this modern age of traffic accidents, patients often are brought to the hospital in an unconscious condition, remaining thus for hours and even for days. It is always advisable to catheterize such patients within a few hours, leaving a retention catheter in place until the patient is able to void voluntarily. Although catheterization of the bladder carries with it the possibility of introducing infection, with care, this danger can be minimized. More harm frequently is done by allowing the bladder to become overdistended or improperly emptied. Many serious conditions of the upper part of the urinary tract are directly traceable to obstruction to the flow of urine through the urethra. The commonest of these conditions are hydro-ureter and hydronephrosis associated with secondary infection of the kidneys and bladder; as in cases of chronic hypertrophy of the prostate gland or stricture of the urethra such conditions may produce renal damage with resultant uremia.

As a rule, this type of uremia rapidly disappears if a free flow of urine is established and if the intake of fluids by mouth is increased to 3 or 4 liters a day, supplemented by intravenous administration of a solution of 0.9 per cent sodium chloride, if necessary.

UREMIA

Although uremia is gradual in its onset, many times its existence is not suspected or detected until it has developed to an advanced stage. Often, a patient is in coma when a physician is called. The uriniferous odor of the patient's

breath and body permeates the room and usually is an indication of the condition present. However, the uriferous odor of the uremic patient occasionally has been confused with the peculiar odor associated with diabetic acidosis; therefore, one should not rely on this method of diagnosis alone. A history of low urinary output, usually with some edema, nausea, vomiting, increasing malaise, and fatigability is important. Generally, a history of previous renal disease is obtained. Conditions that most frequently are associated with suppression of renal function to the point of uremia are: nephritis, pyelonephritis, vascular lesions of the kidney; polycystic kidney, cirrhosis of the liver, amyloid disease; malignancy of the kidney, tuberculosis of the kidney; infiltrating malignant or very large benign lesions of the pelvis; poisoning owing to mercury, lead, arsenic; acute toxic reactions following scarlet fever, tonsillitis, mastoiditis; pneumonia, peritonitis, and other post-operative complications.

Frequently, uremia occurs when there is a fair urinary output, the so-called dry uremia so often encountered in association with late hypertensive cardiovascular renal disease and with chronic glomerulonephritis. The urine is clear and of fixed, low specific gravity, usually not over 1.012 and not less than 1.007 or 1.004. Although the kidneys are able to excrete water, they are not able to concentrate or to excrete the waste products of metabolism in sufficient amounts; these accumulate in the blood and throughout the body to such a degree that toxic reactions occur. However, if sufficient water can be "run" through such kidneys, such patients may live for months or years in spite of rather high concentration of blood urea. It is amazing how well these patients tolerate an abnormally high concentration of blood urea; this observation makes it doubtful as to whether it is the urea itself that has toxic properties or whether some parallel toxic substance, not yet detectable, exists coincidentally.

Treatment of uremia complicated by edema presents a much more difficult problem. In this type of case, fluids cannot be given freely and treatment with diuretics, as a rule, is not very successful. If uremia is encountered, the CO_2 combining power should be estimated, as there is frequently an associated acidosis which needs treatment. Occasionally, these

patients have a low blood calcium which produces no symptoms until the CO_2 combining power is raised by administration of alkali. It has been demonstrated in Snapper's clinic in Amsterdam that when acidosis exists, more free calcium is released and it is thought that this may be the mechanism in acidosis that suppresses the tetany associated with low blood calcium. Recently a case of uremia associated with acidosis and with low blood calcium was observed; no signs of tetany appeared until administration of alkali had raised the CO_2 combining power above the level of acidosis. Low blood calcium is observed frequently when the serum protein is low and, in such instances, does not seem to produce any symptoms of calcium deficiency. This complication can be overcome by administration of calcium gluconate intravenously, or calcium lactate can be given three times a day in doses of a heaping teaspoonful dissolved in hot water. Viosterol or other products containing vitamin D such as cod liver oil or haliver oil should be given with the calcium.

In treatment of uremia without edema, the patient should be encouraged to drink all the water that he can take comfortably. If vomiting is a complicating symptom, it is often necessary to supplement fluids intravenously. Administration of 1,000 c.c. of a solution of 0.9 per cent sodium chloride once or twice a day intravenously is preferred by some. A solution of 10 per cent d-glucose, 1,000 c.c. once or twice a day, may be given. A solution of 5 per cent d-glucose and 0.5 per cent sodium chloride is very desirable and does not cause reactions. It is a good policy to give not more than 2 liters of fluid intravenously in a day, one in the morning and one in the afternoon, and it is much safer to give only 1 liter a day by intravenous injection, especially if this method of therapy is to be continued for several days. It should be given slowly over a period of one and a half to two hours. If any pulmonary symptoms such as tightness in the chest, coughing, dyspnea, pounding of the heart, and so forth should develop, intravenous treatment should be stopped at once. Occasionally, cardiac failure with pulmonary congestion is brought about by too enthusiastic administration of intravenous fluids and causing more harm than good. By adding 10 c.c. of aminophyllin (4.5 grains) to the solution of intravenous fluid it is thought that cardiac reac-

tions are fewer. Should edema develop, the patient's weight increase rapidly, râles appear in the lungs, fluid accumulate in the chest or abdomen, or signs of cardiac decompensation become apparent, intake of fluid and, especially, intravenous administration of fluid should be curtailed.

In treatment of uremia with edema, it is best to try concentrated solutions of d-glucose, such as 500 c.c. of a 20 or 25 per cent solution, given slowly. Aminophyllin may be added to this solution. The milder diuretics such as potassium nitrate can be tried, giving 4 to 8 gm. a day in enteric-coated pills, as in treatment of any edema. If nausea or vomiting are complicating factors, it is practically impossible to give potassium nitrate by mouth. It cannot be given intravenously.

Occasionally, cases of uremia with edema and low serum protein are encountered. In these cases successful results have been obtained by giving 500 c.c. of a 6 per cent solution of acacia intravenously for three administrations. By so doing, edema is reduced and the patient is able to take and to eliminate more water, thus reducing his edema more satisfactorily.

The diet usually is not important in treatment of uremia. The appetite is usually poor and vomiting is a common symptom. Attractive, appetizing food should be given, keeping the content of protein around 50 gm. a day and the content of salt and of condiments low. Foods of high caloric value should be selected so that the volume of food ingested will not be too great.

RENAL COLIC

Usually, ureteral colic is not a dangerous situation. Danger exists, however, in mistaking it for some other more serious condition. When a physician is called to see a patient who has severe abdominal pain, he cannot be sure, merely by noting the type, location, and radiation of the pain, whether the patient has renal colic, gallbladder colic, strangulated hernia, appendicitis, or some other acute condition. It is advisable, however, if the pain is agonizing, to give the patient a hypodermic injection of $\frac{1}{6}$ grain to $\frac{1}{4}$ grain (0.01 to 0.016 gm.) of morphine with $\frac{1}{100}$ grain (0.0006 gm.) of atropine to ease his suffering. Usually, no fever and only moderate abdominal tenderness accompanies ureteral colic. There is often nausea and vomiting. As a rule,

urinalysis will give evidence of blood and, often, pus. Roentgenologic examination of the kidneys should be made. Frequently, intravenous urography will give evidence of a stone in the ureter and dilatation of the portion of the ureter above the obstructing stone. Many of these stones, if not too large, can be removed by manipulation through the cystoscope. Some cases require ureteral lithotomy.

PYELONEPHRITIS

Frequently, this condition develops with violent and alarming symptoms and, until the last few years, treatment was not very successful. The onset is heralded by frequency and burning in voiding, violent chills, and fever as high as 102° to 105° F. (38.8° to 40.6° C.). There may be pain and tenderness in one or both renal regions, depending on whether the infection is bilateral or unilateral, and in the region overlying the bladder. The urine is loaded with pus and organisms and, frequently, gross or microscopic hematuria is present. The organisms usually present are *Escherichia coli*, streptococci, and organisms of the genus *Aerobacter*. Many other types of organisms also are found. It is very important to culture the urine obtained from these patients by catheterization and to identify the type of organism present, in order that a suitable urinary antiseptic can be employed.

A few years ago, the ketogenic diet was used in combating these infections. Such treatment was very successful especially in dealing with *Escherichia coli*. Later, this was displaced largely by use of preparations of mandelic acid. Now, with the introduction of sulfanilamide, a combination of urinary antiseptics is available that greatly enhances the patient's chances of recovery.

As a rule, the best results with preparations of mandelic acid are obtained with *Escherichia coli*. It is important that the pH of the urine be maintained at about 5.5. This can be done by giving ammonium chloride in enteric-coated pills of 0.5 gm. each; four of these are given three times a day after meals. However, by use of 3 drachms of elixir of ammonium mandelate four times a day, need for acidification is eliminated in about 90 per cent of the cases. Usually, treatment for a week or ten days is sufficient to rid the patient of bacilluria

caused by *Escherichia coli*. A second or third course of treatment may be given later, if necessary. Daily microscopic examination and frequent culture of the urine are made. Medication is continued a day or so after the organisms have disappeared from the urine.

If the streptococcus is the invading organism, sulfanilamide appears to be the urinary antiseptic of choice. With its administration, it is not necessary to acidify the urine. To the adult patient 40 grains (5-grain tablets) are given the first day, 60 grains the second and, if well tolerated, 90 grains are given the third day; the dosage is reduced to 60 grains and 40 grains respectively the next two days. Many patients do not tolerate sulfanilamide well. Nausea and vomiting, or even more toxic reactions such as dermatitis, blurred vision, acute myopia, pain in the region overlying the bladder, diarrhea and headaches may develop. It is important to make frequent leukocyte counts to be certain that there is no depression of these. These symptoms rapidly disappear on discontinuing treatment and seldom cause serious concern. Should such signs or symptoms occur the medicine should be withdrawn and large amounts of fluid should be given.

It is well to determine the condition of the renal calices, renal pelves, ureters, bladder, and urethra by intravenous urographic and by cystoscopic examination of these cases. Frequently, stones, hypertrophy of the prostate gland, or other obstructing lesions that are present cause secondarily hydro-nephrosis, hydro-ureter and other complicating factors demanding specific attention urologically. If urethritis exists, it should be treated with a 5 per cent solution of protargol (strong silver-protein) and, if the bladder is inflamed, it should be irrigated daily with a solution of boric acid or a solution of potassium permanganate, 1:8000. This may be followed by instillation of 1 ounce of an emulsion of 7 per cent silver iodide. For such complications a competent urologist should be consulted. Often, in these cases, renal inflammation and damage is sufficient to result in retention of metabolic end products and uremia. If this occurs, treatment should be the same as in any case of uremia, as described elsewhere in this discussion.

COMMON EMERGENCIES ARISING IN THE COURSE OF HEPATIC DISEASE

HUGH R. BUTT

DISEASES that involve the liver are noted for their latency and chronicity rather than for the emergencies that develop in their course. The great regenerative capacity of the liver, its extraordinary physiologic reserve and its remarkable tolerance of injury suffice to make acutely dangerous situations relatively uncommon.

Among the common emergencies may be mentioned the collapse that sometimes follows abdominal paracentesis, the hemorrhagic diathesis, and hepatic insufficiency. The rôle of the liver as the commissariat of the body and its importance in regulation of the chemical composition of the blood make knowledge of hepatic physiology a prerequisite to successful treatment of such emergencies.

HEPATIC INSUFFICIENCY

Hepatic insufficiency may occur at any time in the course of chronic disease of the hepatic parenchyma. Following operations, particularly those performed on the biliary tract, hepatic insufficiency is an extremely serious complication. It may also supervene when either acute or subacute forms of atrophy of the liver are present and in the course of chronic conditions such as cirrhosis.

Occasionally, the patient who has chronic atrophy (or cirrhosis) and who has remained in reasonably good health for several years, suddenly may give evidence of hepatic failure. Frequently, such episodes will follow abdominal paracentesis or an operation of any type, particularly if anesthesia is required. Taking of alcohol, the presence of infection, subjection to undue exposure, or indiscretions in diet may precipitate hepatic insufficiency. When obstruction of the common bile

duct occurs, no matter whether the obstructing agent is a calculus, a cicatrix, or a neoplasm, the danger of acute failure of the liver remains one of the preëminent considerations. This danger, for reasons as yet unknown, is amplified greatly by performance of an operation.

The clinical syndrome called "acute liver insufficiency" or "acute hepatic insufficiency" is a fairly definite picture. The term is used loosely to describe failure of the liver in one or more of its metabolic functions but its nature is as obscure as is that of its companion, uremia. Often this syndrome is ushered in by deepening icterus, weakness and restlessness which progress rapidly until mental confusion and coma supervene. At times, these latter symptoms are comparable with those of active encephalitis and various pathologic reflexes are present which suggest that involvement of the central nervous system has occurred. Frequently, progressive oliguria, orthopnea, cyanosis, and rapid increase in the amount of edema and ascites occur.

It is rather significant that the symptoms of acute hepatic insufficiency observed among human beings are comparable with those of hepatectomized experimental subjects, although the respective chemical disturbances associated with the condition are not in accord. From the work of Mann and Magath^{12,13,14} and others, it is known that the most conspicuous effect of total removal of the liver is rapid decrease in the concentration of blood sugar accompanied by loss of reflexes, muscular twitching, convulsions and death. If the hepatectomized subject is kept alive by intravenous administration of a solution of d-glucose, it is observed that the formation of urea, deamination of amino-acids and destruction of uric acid cease; retention of indirectly reacting bilirubin also occurs. All these chemical phenomena are absent in the clinical subject who has hepatic failure, although isolated instances of one or more such disturbances have been recognized. Bockus reported two excellent examples, namely, two patients who had hepatic insufficiency and who died owing to hypoglycemia. The clinical picture depends, as Bollman has suggested, on failure of the liver to deal with certain endogenous and exogenous toxins. This detoxicating function of the liver is impaired easily and its failure undoubtedly figures largely as a

cause of so-called hepatic deaths. That this function is involved is illustrated adequately by the inability of the liver to conjugate hippuric acid from benzoic acid and glycine. Whether or not the frequent coincidence of renal insufficiency results from failure of this detoxicating function, is not known.

Treatment.—If one may assume the correctness of the above facts, treatment of hepatic insufficiency is a somewhat less hopeless matter than it would be if the primary metabolic functions of the liver were known to be lost. Since regeneration of hepatic tissue occurs rapidly following partial removal of the liver and following sublethal injury by some toxic agent in normal experimental subjects, it is essential to use every proper means to maintain life until some restoration of hepatic function occurs.

The first principles of therapy are to dilute and to eliminate toxic agents and to attempt to restore the normal glycogen content of the liver. Experimentally, Bollman and Mann and others have noted that reaction of the liver to toxic agents varies with the diet of the subject and with the chemical composition of the liver; a liver that has a high content of glycogen appears to be more resistant to toxic agents than does a liver that contains a high percentage of fat. Thus, the rational basis for therapy with glucose is based on the belief that such therapy increases storage of glycogen and favors regeneration of the parenchyma of the liver.

Maintenance of a high content of glycogen in the liver is accomplished best, if possible, by feeding the patient a diet high in carbohydrate and low in fat and protein. Such a diet should contain about 250 to 393 gm. of carbohydrate, 58 to 60 gm. of protein, and 60 gm. of fat, equivalent to 2,200 to 2,344 calories. The average patient cannot consume this much food and it is, as a rule, necessary to administer d-glucose by vein. Usually, 2,000 c.c. of a solution of 5 per cent d-glucose in physiologic solution of sodium chloride is an adequate daily dose but larger amounts or a more concentrated solution may be required. For example, the individual in coma caused by hepatic disease may require continuous intravenous injection of a solution of 5 per cent d-glucose in physiologic solution of sodium chloride, while a solution of 10 to 20 per cent d-glucose in physiologic solution of sodium chloride may be used if the

patient's veins are in good condition and if edema or ascites complicates the picture.

Jones has presented some interesting clinical evidence in support of intensive therapy with d-glucose in cases of hepatic failure. In the "preglucose" era, during a period of eight years, 95 per cent of twenty-four treated patients died. In the years 1930 to 1935 inclusive, thirty-two additional patients were treated; of these, twenty died; this represents a mortality of 63 per cent. Of this latter group, among the patients who received solution of d-glucose intravenously for ten days or longer the mortality was only 22 per cent. Bollman has repeatedly demonstrated that administration of d-glucose will bring about recovery of experimental subjects that have cirrhosis, induced by administration of carbon tetrachloride, even after the stage of ascites has been reached.

Patients in coma of hepatic origin who do not give evidence of improvement following employment of the usual methods of treatment, have been found to respond to administration of sodium r-lactate with some degree of success. Snell administered this material, in doses of 10 to 20 gm. in 1,000 c.c. of 10 per cent solution of d-glucose in physiologic solution of sodium chloride, to a group of twenty-six patients representing various types of hepatic disease. However, only 25 per cent of the patients gave any definite evidence of improvement. He cautioned that since administration of sodium r-lactate is followed by formation of excess base, the values for the combining power of carbon dioxide, for blood urea and for plasma chlorides should be checked frequently to avoid development of serious alkalosis.

Frequently individuals who have hepatic insufficiency give evidence of the presence of oxygen want, as is shown by the presence of cyanosis, of hyperpnea and of measurable unsaturation of the arterial hemoglobin. As many workers have shown, this favors further disintegration of the parenchyma of the liver. This anoxemia depends on a reduced affinity of hemoglobin for oxygen, as has been pointed out by Keys and Snell. Oxygen therapy is not always necessary but often, after placing a comatose patient in an oxygen tent, definite improvement may ensue. Failure to administer oxygen to these individuals early in the course of hepatic insufficiency is, perhaps

a common error. It should be noted that transfusions of whole blood correct this anoxemia temporarily and the additional hemoglobin favors transportation of a more adequate supply of oxygen to the tissues.

Transfusions of whole blood are not only of great importance in supplying hemoglobin for transportation of oxygen, but they are also of equal value in maintaining an adequate volume of blood. To effect a relatively constant equilibrium between blood and tissue fluid requires maintenance of the colloidal osmotic pressure of serum and, for this purpose also, whole blood is of great value. Repeated administration of small transfusions (250 c.c.) of whole blood appears to be more satisfactory than that of larger transfusions and, when blood has not been available, solution of acacia has been used as a satisfactory substitute (Butt and Snell, 1937). Intravenous injection of a solution of 6 per cent acacia in a physiologic solution of sodium chloride has been definitely shown to raise the colloidal osmotic pressure of the blood serum, a factor which, in turn, may aid in initiating normal excretion by the kidney.

Among certain individuals decrease in the concentration of chloride in the blood has been encountered. The nature of this loss of chloride is not clear; doubtless it depends on some abnormal distribution of electrolytes between blood and tissue fluids. These low values for chloride are, at times, extremely resistant to efforts made to elevate them by administration of sodium chloride by mouth or by vein. Sodium r-lactate, for instance, may induce an even further decrease in the concentration of blood chlorides. A satisfactory theoretical explanation of this metabolic phenomenon is not available at present. The only available therapeutic measures consist in administration of sodium chloride in various ways and in use of the cortical hormone of the adrenal gland to assist in retention of chlorides.

Renal failure commonly accompanies hepatic insufficiency. Presumably, failure of the detoxifying function of the liver throws an added burden on the kidneys. The exact cause of this failure is unknown and treatment of the condition is difficult: decrease of urinary output is always a bad prognostic sign and, conversely, as Jones has pointed out, spontaneous

diuresis which occurs in the presence of hepatic failure indicates that improvement of the patient's condition has occurred and, consequently, the prognosis is improved. Diuretics may be tried but they are usually of little value; in fact, one must avoid strenuous dosing with diuretics because of their possible harmful effect on renal function.

It must be remembered that even when a most severe grade of hepatic insufficiency exists the patient may survive if intensive treatment is instituted. Available clinical data indicate that preservation of a high reserve of glycogen in the liver, maintenance of a normal volume of blood by administration of transfusions of whole blood and adequate oxygenation of the blood to maintain optimal conditions of tissue respiration are of prime importance in treatment of hepatic insufficiency. Analysis of these data further reveals that there are reasonable prospects of benefit to the patient even when advanced hepatic damage exists. Not only may the patient survive, but also a high degree of recovery of hepatic function may supervene if intensive, persistent treatment is carried out. Adoption of a pessimistic attitude toward these patients who are suffering from hepatic failure leads to half-hearted treatment and thus to unnecessary deaths. By sheer persistence in treatment many unexpected recoveries occur. This is illustrated well by one case observed at the clinic: the patient's brother-in-law, a physician, had administered d-glucose by vein daily for a period of nearly seven months. At the end of that period, in spite of repeated episodes of hepatic insufficiency, the patient was again in normal health.¹⁸ Lack of application of such persistent therapy doubtless accounts for a large number of fatalities from hepatic insufficiency.

HEMORRHAGIC STATES

Methods by which an attempt is made to measure the tendency of a patient to bleed have been as unsatisfactory as have been studies of the mechanism of bleeding. Most determinations of coagulation time and of bleeding time are of little or no value in determining a tendency to bleed and the statement attributed to Ivy still rings true, that the best test for bleeding is in evidence when the patient bleeds.

In association with diseases of the liver two types of hemorrhage may occur: hemorrhage from rupture of dilated veins present in the esophagus or in the stomach and diffuse hemorrhage that occurs particularly in association with obstructive jaundice.

Early diagnosis of a bleeding varix is difficult. It may manifest itself by hematemesis, rarely by melena. Often the only noticeable factor is development of progressive weakness and decrease in the concentration of hemoglobin and in the number of erythrocytes. The presence of varices usually can be demonstrated by roentgenologic examination and, when their presence is ascertained, the best treatment is preventive in nature, that is, treatment is directed toward prevention of hemorrhage in so far as possible. Although spontaneous rupture of varices does occur, indiscriminate use of the stomach tube, uncontrolled vomiting, and coughing are more often the precipitating factors. When hemorrhage occurs from varices, administration of morphine sulfate and frequent transfusions of small amounts of whole blood are indicated. If the abdomen is distended with fluid, paracentesis may help to relieve the increased venous pressure. In a rare instance, the heroic measure of ligating the coronary veins may be successful.

Management of hemorrhage associated with certain types of obstructive jaundice has been impeded greatly by lack of a practical concept as regards clotting of blood. Available evidence indicates that in clotting of blood there are two distinct, consecutive phases: one consists of interaction between prothrombin, calcium, and platelets (or tissue extracts) to form thrombin; the other involves a reaction between thrombin and fibrinogen to form fibrin (Eagle).

The hemorrhagic diathesis is, perhaps, the most feared complication of obstructive jaundice and is the factor chiefly responsible for the increased surgical risk among this group of patients. Its presence is usually recognized when a slow oozing of blood occurs from incised surfaces. Frequently, in the presence of coma associated with hepatic disease or when severe infectious hepatitis is present, spontaneous bleeding may occur from supposedly intact tissues of every organ of the body. Snell and Boland have observed that the greatest danger from this type of hemorrhage is encountered when complete

mechanical blockage of flow of bile into the intestine has occurred. There may be present some premonitory signs such as purpuric spots on the skin or slight oozing from the gums but, more often, such severe hemorrhages appear without warning.

Just why a patient who has jaundice should bleed more easily than does a normal individual has been difficult to explain. Each of the constituents of the blood has been suspected, at one time or another, of being the cause either because it was present in excessive or in deficient amounts or because it occurred in some abnormal form or combination. Recently, Quick and others presented evidence which indicates that in the presence of hepatic disease the abnormality that causes bleeding is owing to the presence of a diminished quantity of prothrombin in the circulating blood. This hypothesis is supported strongly by the results of the experimental work of Hawkins and Brinkhous and of Greaves and Schmidt, who have demonstrated a definite deficiency of prothrombin among animals which develop hemorrhagic tendencies in the presence of biliary fistula.

There are certain recent studies of deficiency of vitamins which have a direct bearing on the concentration of prothrombin associated with hemorrhagic states. Dam and Schönheyder have demonstrated that if chicks are fed diets deficient in certain substances hemorrhage will occur and that the blood of these animals is deficient in prothrombin. If these animals are fed material containing certain vitamin sterols (a mixture tentatively designated as vitamin K), elevation of the low level of prothrombin occurs and is accompanied by decrease of the tendency to hemorrhage. It has been demonstrated further that vitamin K is present in the prothrombin of the normal chick but is absent or is inactive in the chick that has hemorrhagic disease. In short, it appears that a deficiency of the prothrombin in the blood owing to failure of absorption of certain sterols necessary for formation of prothrombin, is responsible for the hemorrhagic diathesis that occurs in the presence of jaundice.

Treatment.—Treatment of this type of hemorrhagic diathesis is largely a matter of prevention. When possible, operative measures to relieve biliary obstruction should be instituted

as promptly as possible after diagnostic studies and suitable preoperative preparation have been completed.

Intravenous administration of solution of d-glucose is regarded as essential to preoperative preparation and 5 c.c. of a 10 per cent solution of calcium chloride may be added to the solution of d-glucose. Although there is no good evidence that a deficiency of calcium exists under these conditions, most physicians who treat large numbers of patients continue to use this form of treatment. At least, such treatment carries with it the assurance that an excess of at least one of the constituents necessary in the clotting of blood is present. In addition, Carr and Foote have demonstrated that the presence of an excess of calcium chloride appreciably inactivates sulfydryl anticoagulants *in vitro*; the same action may occur *in vivo*. These sulfur-containing compounds are known to accumulate in the blood of patients who are jaundiced and it is conceivable that calcium salts may inactivate sulfur-containing compounds *in vivo*.

Repeated transfusion of whole blood is probably the most valuable single measure employed. A single transfusion of blood seldom will decrease the tendency to bleed for longer than six to fifteen hours, yet, during this period, the patient may have recovered from the tendency toward hemorrhage. Transfusions of plasma have been used, but they appear to have no advantage over transfusions of whole blood.

That absence of bile in the intestine might be a factor in production of these hemorrhagic states was suggested by Judd, who frequently fed bile by tube to patients who had obstructive jaundice. Wangenstein has noted also that administration of bile to patients seemed to be of definite benefit in prevention of hemorrhage. This is certainly a very important clinical observation and it is supported adequately by the results of the experimental work of Hawkins and Brinkhous and of Greaves and Schmidt. It is not known whether bile itself supplies some factor necessary for clotting of blood or whether bile aids in absorption of factors essential for normal coagulation. Experimental data would indicate that, more likely, the latter suggestion is probably true. In any event, this therapy is so simple that it should be tried in every case of obstructive jaundice. If whole bile is not available, bile salts may be used.

In addition to the therapeutic measures already mentioned, a variety of procedures have been advocated for relief of the hemorrhagic tendency associated with jaundice. Irradiation of the spleen was advocated by Stephan, but this treatment, in general, has been discarded. Some investigators have used intramuscular injections of the subject's own blood in doses of 50 to 100 c.c. with varying degrees of success. Use of various anticoagulants has been advocated but, on the whole, all are inferior to transfusion of whole or citrated blood.

COLLAPSE FOLLOWING PARACENTESIS

Withdrawal of ascitic fluid frequently is necessary in the course of certain types of hepatic disease. Following paracentesis, circulatory collapse does not occur with any degree of regularity. However, the possibilities of such an occurrence do exist and should be borne in mind.

That such a collapse can occur has been emphasized by Wangensteen and Scott, who were able in the experimental laboratory to produce an immediate fall in blood pressure following sudden decompression of the abdomen distended by fluid. To obviate collapse of the patient consequent on too rapid removal of the transudate, certain prophylactic precautions should be instituted. The blood pressure of the patient should be recorded frequently in the course of every paracentesis. Often this is the only necessary precaution. Some physicians place a binder around the abdomen at the beginning of paracentesis and gradually tighten it as fluid is withdrawn. Administration of a physiologic solution of sodium chloride by vein or administration of posterior pituitary extract subcutaneously just before paracentesis is begun decreases the incidence of collapse of experimental subjects. If collapse occurs, the standard measures for elevating the blood pressure should be employed.

PORTAL OCCLUSION

This is a rare complication and of the thirty-two cases of suppurative thrombosis of the portal vein or of its tributaries reported by Weir and Beaver, in only nine was there evidence that a primary lesion which might have been an etiologic factor

existed in the liver. Almost invariably termination is fatal. There is available no satisfactory treatment.

SUMMARY

Judging from experimental data one can assume that the liver is very resistant to repeated injury and that it possesses a remarkable power of regeneration. However, rarely does it fail completely in one or more of its metabolic functions, but frequently it is so severely damaged that the syndrome of hepatic insufficiency appears. This seems to result from inability of the liver to detoxify certain specific toxic substances.

In treatment of hepatic insufficiency, the first principles of therapy are to dilute and eliminate toxic agents and to attempt to restore the normal content of glycogen in the liver. To relieve oxygen want, to supply necessary hemoglobin and plasma protein, to maintain the normal concentration of electrolytes of the blood, to stabilize the acid-base equilibrium of the blood, and to maintain adequate renal elimination are also objectives toward which intensive treatment is directed.

Of the two types of hemorrhage which may occur during the course of hepatic disease, the diffuse hemorrhage that occurs particularly in the presence of obstructive jaundice or of advanced atrophy of the liver is encountered most frequently and is the most serious type of hemorrhage. Recent evidence would indicate that a deficiency in the concentration of prothrombin in the blood which, in turn, is owing to failure of absorption of certain sterols necessary for formation of prothrombin, is responsible for occurrence of the hemorrhagic diathesis in association with jaundice. Whole bile or bile salts offer therapeutic possibilities.

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DIAGNOSIS AND TREATMENT OF EMERGENCIES ASSOCIATED WITH DISEASES OF SOME OF THE DUCTLESS GLANDS

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DISEASES of the ductless glands usually produce chronic and slowly progressive disturbances in physiologic function. If the disease happens to progress rapidly, or if the various mechanisms which compensate for the resulting pathologic physiology suddenly fail, situations arise which terminate fatally unless prompt, vigorous treatment is instituted.

The diseases which must be considered in this connection, roughly arranged in the order of their frequency of occurrence, are: (1) diabetic acidosis and coma, (2) hypoglycemia, induced or spontaneous, (3) the crisis of exophthalmic goiter, (4) the crisis of Addison's disease, and (5) acute parathyroid insufficiency. It is a curious and an unfortunate fact that, in the first four of these conditions, gastro-intestinal symptoms may be conspicuous and, consequently, may overshadow the less spectacular but more diagnostic symptoms which are indicative of the organ that is at fault.

DIABETIC ACIDOSIS AND COMA

Pathologic Physiology.—Profound knowledge of chemistry is not essential for comprehension of the fundamentals in the disturbed mechanism which is responsible for diabetic acidosis and coma. In the human organism, the pancreatic hormone known as insulin is necessary for utilization of all foods. In its absence, all ingested starch and sugar appear in the urine in the form of glucose. Furthermore, approximately one-half (by weight) of the protein in the food, or, for that matter, the protein of the body which is utilized to maintain life during periods of starvation, consists of glucose or compounds changed to glucose; this glucose in the absence of insulin, likewise, is excreted in the urine. Finally, when glucose is

not utilized, the oxidation of ingested fat or body fat is incomplete. Instead of being converted into harmless carbon dioxide and water the oxidative processes stop short of this point and the fat yields various toxic, acid residues, such as acetone, beta hydroxybutyric acid, and aceto-acetic acid. These can be lumped together under the term "ketone bodies." Ketone bodies are probably formed in the liver and are thence excreted in the urine. Before being excreted in the urine, they are neutralized by the alkalis of the tissues and blood. These alkalis or bases consist of sodium bicarbonate and various salts of potassium, calcium and magnesium.

Formation of small amounts of ketone bodies is readily tolerated but formation of large amounts, such as occurs in severe diabetic acidosis, results in continuous excretion of sodium salts and other bases in the urine.* At first only the tissues are affected by this loss of base, and the chemistry of the blood remains unchanged. Finally, when the stores of base in the tissues are depleted, the sodium content of the blood is drawn on to maintain neutrality. Furthermore, both neutralized ketone bodies and sugar must be in solution before they can be excreted by the kidneys. The result is that in their excretion there is a tremendous loss of water. Associated with loss of water there is also for various reasons not entirely understood a loss of chlorides. Finally, when all compensating mechanisms fail, the alkalinity of the blood is decreased and eventually the blood becomes slightly but definitely acid in reaction. It is not understood entirely, nor, for practical purposes, is it necessary to understand, how changes in the blood produce the characteristic symptoms of diabetic acidosis and coma.

The extent of these chemical changes can be determined to a considerable degree by analyzing the blood for its combining power with carbon dioxide, for, if the sodium of the blood has been lost through the kidneys, or has been held in combination with strongly acid ketone bodies, obviously it cannot combine with carbon dioxide and, as a consequence, the carbon dioxide combining power is reduced. Clinically, the degree of hyperpnea or air hunger parallels roughly the loss of carbon dioxide

* For present purposes the rôle played by ammonia in compensating the disturbed acid-base equilibrium that occurs in diabetic acidosis can be neglected.

combining power of the blood; the degree of unconsciousness, however, need not.

Thus far, nothing has been said regarding the blood sugar. This omission has been deliberate because of the usual tendency to overemphasize its importance. It is true that, if acidosis occurs in an untreated diabetic patient, the blood sugar almost invariably is definitely or markedly increased. It is equally true, however, that this increase is not necessarily a measure of the severity of the intoxication. Thus, a patient in deep coma may or may not have an unusually high blood sugar and, conversely, a patient who has a very high blood sugar may not be in coma, or even in acidosis. A sharp reduction of the carbon dioxide combining power of the blood, on the other hand, is tolerated poorly and, almost invariably, is indicative of impending trouble.

Etiology.—Acidosis and coma may occur among severe diabetic patients either as a natural consequence of the disease when treatment is inadequate or as the result of some coexisting disease. Among elderly patients who have mild diabetes, acidosis and coma almost never occur in the absence of associated disease or complication. Most cases of diabetic coma are preventable. When it does occur, generally it can be attributed fundamentally to ignorance or neglect, or to both. Unfortunately, this indictment sometimes applies to the physician as well as to the patient. Breaking the diet, omission of insulin, insufficient amounts of insulin, or some complicating condition such as infection, fracture of a bone, or hyperthyroidism are the usual precipitating factors. Failure on the part of the patient taking insulin to realize that insulin is necessary whether or not he takes food is a particularly common cause of coma. Such patients often are well instructed, conscientious, healthy, and well nourished diabetics who are getting along splendidly. In the presence of an intercurrent infection, they may lose their appetite and may fail to eat. Under these circumstances, the fear of an insulin reaction may lead them to omit their insulin. They fail to realize that as soon as ingestion of food ceases they begin to draw on their store of foodstuffs eaten in the past. This food cannot be utilized in the absence of insulin and, being mostly fat, it rapidly yields large amounts of ketone bodies. Furthermore, in

the presence of infections and other complications, the efficiency of insulin, unit for unit, is decreased. Thus, they are omitting insulin at a time when they most need it. As a consequence, severe acidosis may appear within several hours, and, if it is not recognized promptly as such and if it is not treated, coma develops.

If vomiting does not occur as a result of the initial complication, it is almost certain to appear later as a result of the acidosis. In either event, vomiting accelerates the downward course of the patient. Among diabetic patients, vomiting is always a signal of danger which never should be ignored.

Symptoms and Diagnosis of Diabetic Coma.*—The initial manifestations are notoriously so vague and deceptive that acidosis should be suspected whenever any unusual symptom or sign makes its appearance in a known diabetic patient. Weakness, headache, thirst, anorexia, vomiting, apathy, drowsiness, pains in the legs, back and abdomen are among the more frequent earlier symptoms. Later, dehydration, deep breathing, somnolence, and coma develop. Eventually, the respirations may become irregular and shallow.

Diagnosis of diabetic acidosis and coma should be suspected at the bedside and should be verified by chemical analyses of the urine and, if possible, of the blood. Almost without exception, the urine contains large amounts of sugar and will give a strongly positive test for diacetic acid with ferric chloride. These tests can be made readily in the home. The amount of sugar of the blood is increased and the carbon dioxide combining power is reduced. As previously stated, elevation of the blood sugar may not parallel the clinical condition of the patient but, usually, there is some parallelism between the carbon dioxide combining power and the condition of the patient. Definite symptoms do not begin until the carbon dioxide combining power is below 40 volumes per cent and may not appear until it has decreased to below 30 volumes per cent. If the carbon dioxide combining power is below 20 volumes per cent,[†] the symptoms are generally marked, but the degree

* For the differential diagnosis of diabetic coma and hypoglycemic shock see the section headed "Diagnosis and treatment of hypoglycemic states" in this paper.

† Joslin states that when the carbon dioxide combining power of the blood is below 20 mg. per cent the case should be classified as diabetic coma.

of unconsciousness present does not appear to be related to further reduction in carbon dioxide combining power.

A great deal can be inferred from the appearance of the patient. Generally the cheeks are flushed, respirations are deep, the skin is dry, and the eyeballs are soft. The tongue is red and dry, the oral secretions are tenacious and viscid. Frequently, a distended stomach is in evidence or can be demonstrated by palpation or percussion. The tendon reflexes are reduced or absent and Babinski's sign cannot be elicited.

One should not be deceived by the presence of albumin and casts in the urine or by an elevation of the blood urea, both of which occur with considerable regularity in diabetic acidosis. Leukocytosis, as a rule, is associated with diabetic coma and, in itself, is not indicative of the presence of infection.

Treatment.—Treatment of diabetic coma calls for prompt administration of insulin and replacement of excreted water and electrolytes. Detailed application of these two principles unfortunately cannot be reduced to fixed, didactic rules; nevertheless, it is advantageous to have in mind some sort of standard program which can be modified to meet the exigencies in any specific case. The general plan employed at The Mayo Clinic at the present time was introduced by Wilder and has been followed with only minor changes ever since.

Too much emphasis cannot be placed on the necessity of considering each patient in diabetic coma as a specific problem in therapeutics. For example, children in coma must be treated somewhat differently from adults, a patient who has an uncomplicated coma differently from one suffering from a serious infection, and so forth. In every instance, the response to initial treatment must serve as a guide to the intensity with which further treatment is pursued.

Whenever possible, patients in diabetic coma should be treated in a hospital where facilities are available for chemical analysis of the blood, provided that too much time will not be consumed while the patient is en route. Treatment, however, can and should be instituted before the patient is moved and arrangements should be made for continuation of treatment if the journey will require more than four hours. The promptness with which treatment is started is one of the biggest single factors in prognosis. Consequently, it is wise to

notify the hospital to expect the patient so that preliminary arrangements can be made.

There are many similarities between the pathologic physiology of shock and of diabetic coma, and the adjuncts to treatment are the same in both. For example, if possible, the bed should be warmed before the patient is admitted to the hospital and afterward the heat of the patient's body should be conserved by use of blankets and hot water bottles. The latter should not be placed near the feet because of the danger of burning the patient. Gastric lavage with a warm solution of 5 per cent sodium bicarbonate should be done routinely (unless the patient appears moribund), even though the patient may have vomited recently. Generally, there will be an appreciable amount of material found to be present in the stomach and its removal greatly facilitates subsequent feedings by mouth. After the stomach has been emptied, 250 to 500 c.c. of the solution of sodium bicarbonate may be left in it. A cleansing enema should be given routinely.

While these procedures are being carried out, blood should be drawn for analysis, insulin should be given, and arrangements should be made for administration of fluids. The physician, if he has not done so already, should try to find out why diabetic coma occurred. Was it the result of overeating, failure to take sufficient insulin, omission of insulin, previously unrecognized diabetes, or was it, possibly, the result of an obscure infection or other complication not as yet evident? If no satisfactory explanation can be found, he should be highly suspicious of some cryptogenic infection or other complication and should begin to search for it promptly. In this connection, such possibilities as hyperthyroidism, pyelonephritis or allied infections of the urinary tract, and acute appendicitis should be taken into consideration.

Dosage of Insulin.—The dosage of insulin is that amount which will accomplish the purpose for which it is given. It will vary according to the age of the patient, the severity and duration of the acidosis, the amount of insulin* that has been given previously and, to some extent, on the duration of the diabetes.

* A severe diabetic patient in coma who would daily require for example, 40 units of insulin, or greater, naturally must be given a larger initial dose than would be given to someone never before treated with insulin.

and the usual dosage of insulin. Provided that the diagnosis has been established, the initial dose will vary from 20 to 100 units or more, depending on the condition of the patient and on the other factors just mentioned. This should be repeated at intervals of thirty to sixty minutes, continuing until the patient shows some signs of improvement. If there is not a definite improvement in three or four hours, larger doses should be given. One should not worry about the total amount of insulin that is used. Most patients who have died in diabetic coma have been undertreated rather than overtreated. There is, of course, some danger (which I think is apt to be overemphasized) that the patient will slip from diabetic coma into hypoglycemia without evincing premonitory signs and symptoms. This happens only rarely and I have never seen a fatality from hypoglycemia when it occurred under such circumstances. Hypoglycemia is usually not fatal and responds quickly to treatment but diabetic acidosis and coma are always potentially fatal and respond to treatment very slowly. Therefore one is usually justified in giving relatively large doses of insulin, even at the risk of producing an insulin reaction, rather than in giving an amount of insulin insufficient to correct the acidosis. As soon as the patient is able to retain fluids by mouth, carbohydrates in the form of sweetened drinks, such as orange juice, ginger ale, or sweetened tea, should be given to "cover" the insulin. One hundred to 200 c.c. of such solutions can be given cautiously in divided doses at regular intervals. If fluids given by mouth are not tolerated well, or if vomiting occurs, their use should be promptly discontinued and 5 per cent solution of glucose be given parenterally, by intravenous injections, proctoclysis or hypodermoclysis.

The insulin used should be "regular," unmodified insulin. Because of its slow action, protamine zinc insulin should not be used except as an adjunct to treatment. An initial dose of 50 units or less (depending on the age of the patient, severity of the coma, and other factors previously mentioned), of protamine zinc insulin can be given and subsequent treatment for the first twelve to twenty hours carried on with regular insulin just as though the protamine zinc insulin had not been used. If it is felt that the insulin given subcutaneously will not be absorbed, regular insulin can be given intravenously. In gen-

eral, however, it is better to give the regular insulin subcutaneously.

Treatment is facilitated greatly if the exact chemical status of the blood can be determined at frequent intervals. If, after treatment has been in progress for four to eight hours, favorable clinical and chemical changes have not occurred, one can be certain that the treatment has been inadequate regardless of how many units of insulin were given. Urinalysis at intervals of one to two hours can be used as the only guide to treatment when the patient is able to void urine at regular intervals. Twenty or 30 units can be given when the urine turns red with Benedict's solution, 15 units when orange, and 5 or 10 units when green. There is reason to believe that repeated small doses of insulin are more effective than single large doses. It is usually inadvisable to catheterize patients repeatedly to obtain specimens of urine because of the danger of producing an ascending infection of the urinary tract.

Fluids.—Patients in diabetic acidosis or coma invariably are dehydrated severely. Quick restoration of the blood volume and tissue fluids is imperative. The best way to accomplish this is by use of saline solutions intravenously.* Two to three thousand cubic centimeters can be given in this fashion and the administration of fluids continued by mouth, by hypodermoclysis, or by proctoclysis. In a severe case, 7,000 c.c. or more of fluid may be given in the first twenty-four hours. The initial intravenous injection of 1 liter of fluid may be given fairly rapidly. Subsequent injections may and probably should be given more slowly. Some clinicians prefer to give solutions of glucose and saline solutions intravenously at the onset of treatment. I have never been convinced of the necessity of giving glucose intravenously early in the course of treatment, as most patients in coma are pouring out huge amounts of unutilized glucose in the urine. Furthermore, the giving of glucose intravenously early in the course of treatment has the obvious disadvantage of interfering with the evaluation of the efficacy of the treatment at a time when it is very important to know how much effect has been produced by the amount of insulin given. To me, this practical consideration

* Ringer's solution containing the sodium salt of racemic lactic acid has been advocated by Hartman.

carries more weight than the theoretical benefits which might be derived by increasing the amount of utilizable carbohydrates.

Many times the blood sugar drops before the carbon dioxide combining power rises. If the lag in recovery of the carbon dioxide combining power is too great, 250 to 500 c.c. of a solution of 5 per cent sodium bicarbonate may be given intravenously. Ultimately, even if no alkalis are given, the carbon dioxide combining power usually returns to normal, partly as the result of liberated base previously combined with the ketone bodies. Large amounts of bicarbonate are definitely contraindicated. Patients so treated may experience a marked alkalosis with practically no amelioration of the symptoms. In fact, Joslin, whose opinion commands great respect, does not use any alkali in the treatment of diabetic coma. I have never seen the judicious use of alkali produce any recognizably harmful effects. In fact, in a few instances, it seemed to be a crucial factor in recovery.

Circulatory Failure and Anuria.—Circulatory failure is manifested by a falling blood pressure and, possibly, by anuria. Both of these signs usually are an indication of a bad prognosis. Hypertonic solutions of glucose or solutions of 10 per cent sodium chloride given intravenously have been used with success to overcome this condition. Transfusion of blood may be of benefit. If hypertonic solutions are given intravenously, an adequate amount of mobilizable fluid must be present in the tissues. Usually the circulation fails, in part, for the same reason that it fails in shock, namely, because of lack of a sufficient volume of circulating fluid. It may possibly be a result of toxic effects of the ketone bodies on the myocardium. Under such conditions, it is doubtful whether or not cardiac stimulants, such as digitalis, are of any particular value.

Prognosis.—Among younger patients who do not have complications, the prognosis is good provided that adequate treatment has been given. Among older patients, whether or not complications are present, the condition carries a greater mortality rate. Clinical considerations such as the duration of coma, the degree of coma, the age of the patient, and the presence of complications are of greater importance in prognosis than laboratory data. As one might expect, younger patients

do better than older patients; those who have no complications have a more favorable outlook than those who have complications. Dillon and Dwyer found that the mortality rate was highest among those patients who, on admission to the hospital, were so deeply in coma that they could not answer "yes" or "no" to a simple question. But here again even when all indications point to a fatal termination, skillful and vigorous treatment literally may snatch many patients from the grave. Certainly, the indications of an unfavorable prognosis constitute no excuse for indifferent therapy.

The incidence of coma among known diabetic patients in a locality is an index of the quality of the medical services rendered by the profession. Since the advent of insulin the incidence of diabetic coma has been materially decreased, but the fact that it has not been almost completely obliterated indicates either that the instruction given diabetic patients is inadequate or that the medical profession is not taking full advantage of the facilities available for the treatment of diabetes. In either event, if diabetic coma has occurred in a known diabetic patient, in the parlance of the Christian Scientist, "Error crept in."

DIAGNOSIS AND TREATMENT OF HYPOGLYCEMIC STATES

Normally, there is about a teaspoonful of sugar in the blood stream at any one time or, in more precise terms, the normal concentration of the blood sugar ranges from 70 to 120 mg. per 100 c.c. of blood.* If there is a sudden decrease in the concentration of the blood sugar, a variety of symptoms occur, most of which can be interpreted as being the result of a disturbance in the nervous system. Evidence has been obtained from many sources which proves that the production of symptoms does not depend on the absolute level of the blood sugar but upon the rapidity with which the change in the level of the blood sugar occurs, or, possibly, on other unknown factors. In any event, patients may have an extremely low blood sugar and be without symptoms and, conversely, typical symptoms of hypoglycemia have been experienced by patients who had normal or even higher than normal blood sugars.

* The values obtained on analysis depend on the method used and the figures quoted apply to analyses done by the Folin-Wu method.

Hypoglycemia most frequently is encountered among diabetic patients who have taken too much insulin. However, it may occur as the result of a widely diversified group of pathologic processes among individuals who are not taking insulin. No matter what the cause, the symptom complex is essentially the same and is relieved by the same measures. This discussion will be confined to a delineation of the symptom complex and the measures necessary to relieve it. No attempt will be made to present the differential diagnosis or treatment of the various causes of hyperinsulinism, spontaneous hypoglycemia, hepatogenous hypoglycemia, and kindred disorders.

Symptoms of Hypoglycemia.—The symptoms of hypoglycemia vary greatly in different individuals and even in the same individual at different times. They include a host of phenomena ranging from simple paresthesia of the lips to generalized convulsions, fugue states, and maniacal behavior. The milder symptoms such as inward nervousness, weakness, tremor, sweating, and faintness resemble those occurring after injection of adrenalin. These may be followed by or associated with a sensation of ravenous hunger. Sweating is a particularly common occurrence. If the blood sugar is not elevated as a result of the patient's taking food, symptoms referable to the central nervous system that defy classification dominate the picture. Dimness of vision, diplopia, ataxia and drunken behavior, stupidity, excitement, negativism, automatic behavior, delirium, mania, and stupor, all have been noted. Emotional instability ranges from all forms of anxiousness and querulousness to violence. Speech is distorted or the patient may be aphasic. There is a remarkable similarity between the hypoglycemic syndrome and acute alcoholism.* Laughing jags,

* So close is the similarity between hypoglycemic shock and acute alcoholism that patients taking insulin are advised not to trust the diagnostic acumen of the police and are usually given cards which read: "This is to certify that I am a user of insulin subject to insulin reactions; if found in a weakened or unconscious condition call the nearest doctor. In the meantime give me sugar, orange juice, or sweetened fluids. My doctor is..... Phone . . . Address . . . , City..... My diet is . . . gm. carbohydrate, . . gm. protein, . . gm. fat. Insulin, . . . units in A.M., . . . units at noon, . . units P.M." I know of one patient who, when hypoglycemic, had an uncontrollable urge to urinate in public. This peculiar trait resulted in so many arrests that eventually the police learned to know him and to give him orange juice.

crying jags, ugly jags, silly jags, in fact the entire gamut of jags are common to both conditions. As in alcoholism, there is a tendency for each episode to result in a behavior pattern that is characteristic for the individual. Coma, twitching of muscles, and frank convulsions, especially among children, frequently follow. Among some individuals, hemiplegia, palsy of the ocular muscles, and allied phenomena occur in the attack and may persist for a few days to several weeks afterward. Nausea and vomiting are not unusual and refusal to take food is an exceedingly frequent and deceptive symptom during the attack. If examination is possible, it will reveal pallor, beads of perspiration on the face, firm eyeballs, dilated pupils, normal pulse, tachycardia, and, very frequently, a positive Babinski reflex. In most instances, there is a dramatic recovery following ingestion of food or injection of glucose but, occasionally, recovery is delayed long after the blood sugar has returned to normal.

Diagnosis.—From what has been said, it is evident that the diagnosis of hypoglycemia in a nondiabetic individual suffering from hyperinsulinism and allied disorders is fraught with great difficulties and it is small wonder that, in most cases, the initial diagnosis is usually erroneous. Such erroneous diagnoses as brain tumor, cerebral hemorrhage, epilepsy, hysteria, encephalitis, toxic psychosis, acute mania, and delirium are made more often than not when the patient is observed during the hypoglycemic episode. Most individuals suffering from recurring spontaneous hypoglycemic attacks experience initial attacks that are relatively mild; these patients soon learn that the attack can be relieved by food. Consequently, a history of previous milder attacks relieved by food is of great value in arousing one's diagnostic suspicions. A history of attacks occurring before meals or after exercise likewise is obtained frequently. Among some patients, episodes occur early in the morning while they are still in bed. Hypoglycemia should be suspected in patients who seek advice because of recurring episodes of a neurologic or neuropsychiatric character, especially if the episodes tend to occur before meals, after fasting or after exercise and if the patient seems to be well in the interlude between episodes.

To establish the diagnosis it may be necessary to have the

patient fast for twelve to thirty-six hours in order to induce an attack by exercise. A positive diagnosis can be made if it can be shown that (1) attacks can be induced by abstinence from food, (2) that the attack is accompanied by definite subnormal value for the blood sugar, and (3) that the attack can be relieved by administration of glucose. Glucose tolerance curves not only are diagnostic of these conditions but even may be misleading. Consequently the diagnosis of pathologic hypoglycemia should not be made solely on the interpretation of glucose tolerance curves.

Among diabetic patients taking insulin, the diagnostic problem is relatively simple. In such cases any unusual symptom, regardless of how bizarre or atypical it is, should be considered to be an insulin reaction and should be treated accordingly until it can be proved to be otherwise. *The fact that a voided or catheterized specimen of urine happens to contain sugar at the time does not rule out an insulin reaction as the urine may have been in the bladder for several hours prior to the reaction.* With the advent of protamine insulin, the problem of recognizing an insulin reaction has been made more difficult. Reactions in patients taking protamine insulin are apt to be more insidious in their onset and, sometimes, they are more refractory to treatment, especially when not recognized promptly. They also tend to occur twelve to twenty-four hours or more after the injection, instead of three to four hours after an injection of regular insulin. Nausea and vomiting and early morning headache are very deceptive symptoms which occur as the result of protamine insulin hypoglycemia. Reactions following protamine insulin sometimes recur in waves after they have been treated.

In either diabetic or nondiabetic individuals the diagnosis of hypoglycemia can be made with certainty only by showing that the symptoms occurred with a definitely subnormal blood sugar and were relieved by its elevation. If a determination of the blood sugar cannot be made, a presumptive diagnosis of hypoglycemia is justified if the symptoms can be relieved either by food or by an intravenous injection of glucose. Unfortunately, criteria underlying differential diagnosis of diabetic coma and hypoglycemic shock still are not understood universally and for that reason are appended in the tabulation.

TABLE 1

DIFFERENTIAL DIAGNOSIS OF DIABETIC COMA AND INSULIN REACTIONS
(MODIFIED FROM JOSLIN)

	Clinical features.	
	Diabetic coma.	Insulin reaction.
Onset	Slow, days	Sudden, minutes
Causes	Ignorance and neglect	Overdosage
	Intercurrent disease	Delayed or omitted meals
		Excessive exercise before meals
Symptoms	Thirst	"Inward nervousness"
	Headache	Weakness
	Nausea	Sweating
	Vomiting	Hunger
	Abdominal pain	Diplopia, blurred vision
	Dim vision	Paresthesia
	Constipation	Psychopathic behavior
	Dyspnea	Stupor, convulsions
	Florid face	Pallor
	Air hunger	Shallow respiration
Signs	Kussmaul breathing	
	Finally, respiratory paralysis	
	Dehydration—dry skin	Sweating
	Rapid pulse	Pulse normal
	Soft eyeballs	Eyeballs normal
	Acetone breath	
	Normal or absent reflexes	Babinski reflex often present
	Chemical features.	
Urine		
Sugar.....	Positive	Usually absent, especially in second voided specimen
Acetone.....	Positive	Negative
Diacetic acid.....	Positive	Negative
Blood		
Leukocytosis.....	Present	
Sugar.....	350 ± mg.	60 mg. or lower
CO ₂ combining power..	Less than 20 volumes per cent	Usually normal
Urea.....	May be elevated often	Normal
Response to treatment..	Slow	Rapid, occasionally delayed

Treatment.—Treatment of hypoglycemia, fortunately, is simple. If the patient is coöperative, any carbohydrate food given by mouth will promptly abort the symptoms. Glucose can be given intravenously or through a nasal tube into the stomach if the patient is comatose. Difficulties arise if the patient is violent and refuses food. In such cases, 0.5 to 1.0 c.c. of adrenalin given hypodermically will help to solve the problem. A rise in concentration of blood sugar follows, if the liver contains glycogen.

Hypoglycemic death, although uncommon, may occur. There is also reason to believe that a few patients who recover from severe and prolonged hypoglycemic shock sustain permanent injury to the central nervous system. There is good reason for regarding hypoglycemic shock as a medical emergency and treating it accordingly, although experience with unrecognized and untreated hyperinsulinism suggests that, even when untreated, hypoglycemia need not be fatal. In very rare instances, clinical recovery either does not take place or is greatly delayed even after the blood sugar has returned to normal. According to Joslin, the longer the period of unconsciousness, the greater the amount of carbohydrate required by the patient. In one fatal case, 200 gm. of glucose were given subcutaneously and intravenously before the concentration of blood sugar began to rise.

ACUTE ADRENAL INSUFFICIENCY ("ADDISONIAN CRISIS")

If both adrenals are removed from an animal, a characteristic fatal symptom complex ensues. This symptom complex has been shown to be the result of removal of the adrenal cortices and not the result of loss of medullary substance. It can be prevented by administration of potent cortical extracts and rectified by the same means after it has developed. It has been shown further that administration of cortical hormone may not be necessary to achieve these results, provided that the electrolytes of the blood are maintained at normal values.

Acute adrenal insufficiency has somewhat the same relationship to chronic adrenal insufficiency (Addison's disease) that diabetic acidosis has to diabetes. It is a clinical rarity and, for that reason, may be difficult to recognize if the well-known stigmas of Addison's disease in the state of chronicity

such as buccal pigmentation, hypotension, asthenia, and so forth, are absent. Occasionally, it occurs in the newborn as the result of hemorrhages into the adrenal cortices, and it occurs almost invariably in patients at some time during the course of untreated Addison's disease.

The symptoms associated with acute adrenal cortical insufficiency are characteristic, irrespective of the etiology, and are essentially the same whether encountered in study of man or of experimental subjects. For example, removal of both adrenal glands of dogs is followed by a latent period, varying from twelve hours to several days, during which time nothing happens. The dogs then become easily fatigued and apathetic; they refuse to eat and rapidly lose strength and weight. As they decline, they usually go into a coma or semistuporous condition and, just before death, muscular twitchings or convulsions may appear. During the period of survival, there is a progressive decrease in blood pressure, blood volume, consumption of oxygen (basal metabolic rate), and body temperature.

Among human beings, apathy, weakness, hiccup, nausea, and vomiting are almost invariably present. Abdominal pain frequently is present. There is a sharp drop in the blood pressure from its usual level, although the blood pressure may not be subnormal. As the crisis continues, symptoms referable to the central nervous system, such as restlessness, maniacal behavior, stupor, muscular twitchings and the signs of meningeal irritation may appear. Sudden death may occur at almost any time in the course of the crisis.

Simultaneously with or shortly after the appearance of the symptoms just enumerated, changes occur in the physical and chemical character of the blood. In a general way, the severity of these changes parallels the severity of the symptoms. The water content of the blood decreases and, as a consequence, hematocrit readings, determinations of hemoglobin, and determinations of the plasma proteins are increased. The blood urea and nonprotein nitrogen are found to be increased, and renal function is impaired as is indicated by the phenolsulphonphthalein test. Finally, profound changes will be found in the concentration of the various electrolytes of the plasma. The values for total base, sodium, and chloride are markedly

reduced while there is usually an increase in the concentration of the plasma potassium. Although it is not clear why these chemical changes take place, for practical purposes it is sufficient to know that the amount of sodium chloride and water excreted by the kidneys has been greatly increased, and that, as a consequence, the stores of sodium chloride in the tissue spaces and, ultimately, in the blood, are greatly depleted. Furthermore, it has been shown that loss of sodium is considerably greater than the loss of chloride ions.

Experimentally, adrenal insufficiency can be prevented from occurring after adrenalectomy, and can be treated successfully after it has occurred, by giving potent extracts of the adrenal cortex and by replacing the depleted bodily stores of sodium and sodium chloride by intravenous injections of sodium chloride, to which has been added more sodium, such as sodium bicarbonate, sodium citrate, or similar sodium salts of organic acids. Furthermore, it has been found that adrenalectomized animals and patients who have Addison's disease tolerate potassium salts very poorly and, conversely, that treatment is facilitated by restricting the intake of those foods which are rich in potassium salts. The efficacy of the low potassium, high sodium dietary regimen has been proved by the fact that completely adrenalectomized dogs have been kept alive and well indefinitely solely by administration of solutions of sodium chloride and sodium citrate, together with a diet low in content of potassium. Kendall, and others, found that such animals were able to breed and to have normal offspring in spite of the fact that cortical hormone was not used except in the immediate postoperative period.

Adrenal insufficiency in many respects is analogous to parathyroid insufficiency (tetany). The latter can be controlled (temporarily, at least) by giving amounts of the missing factor, the parathyroid hormone, by giving large amounts of calcium salts, and by reducing the intake of foods rich in phosphates: adrenal insufficiency can be rectified by administration of cortical hormone, by giving sodium salts, and reducing the intake of potassium salts in the food.

Diagnosis.—The diagnosis of acute adrenal insufficiency may be easy or difficult to make, depending on the presence or absence of the stigmas of chronic adrenal insufficiency

(Addison's disease). If the patient is known to have Addison's disease, any change in the patient's condition should arouse the suspicion that a crisis is incipient. In the absence of facilities for making chemical studies of the blood, the diagnosis can be proved therapeutically. If the signs of Addison's disease are not present, making a diagnosis will present grave difficulties. In such instances, chemical studies of the blood are practically imperative. A moderately elevated concentration of blood urea and reduced concentration of blood chlorides of a patient who is obviously ill and has gastro-intestinal symptoms, should suggest the possibility of an addisonian crisis, provided no other explanation of the chemical abnormalities, such as high intestinal or pyloric obstruction and traumatic or surgical shock, is evident. As is the case with many of the less common diseases, a "sensitized" mind alert to such possibilities is the first requisite in the making of a diagnosis.

Treatment.—Treatment of acute adrenal insufficiency differs from that of the stage of chronicity as does treatment of diabetic coma from that of ordinary chronic diabetes. The acute phases of both diseases constitute major medical emergencies and the essential principles of therapy of both diseases are the same.

The hormones that are lacking should be replaced and the depleted stores of fluids and electrolytes should be replenished. As in diabetic coma, prophylactic therapy is of the greatest importance. During the stage of chronicity, most patients who have Addison's disease uncomplicated by active tuberculosis can be kept in good health by drinking throughout the day 1 quart or more of a solution containing 1 per cent of sodium chloride and 0.5 per cent of sodium citrate, provided that they adhere to a low potassium diet. A number of patients will require, in addition, small amounts of cortical hormone two or three times a week. As is the case in diabetes, acute failure may develop at any time if the regimen is not followed strictly or if some complicating disease arises. Overindulgence in foods rich in potassium was a frequent cause of crisis before the necessity of a low potassium diet was known. Fortunately, cases of either acute or chronic adrenal insufficiency are still clinical curiosities although the length of life of patients who

have Addison's disease is being prolonged, owing to the effectiveness of modern therapy.

The patient who is in crisis should be put to bed immediately and kept warm. Exertion of any sort should be strictly avoided.* Cathartics and enemas are dangerous and unnecessary. Thirty to 100 c.c. of a potent cortical hormone should be given intramuscularly or intravenously at once and 1 to 2 liters of a solution of sodium chloride and sodium citrate should also be given intravenously. If a solution of sodium citrate is not available, a teaspoonful of sodium bicarbonate (baking soda) may be added directly to the intravenous solution of sodium chloride. If necessary, administration of intravenous solutions and the cortical hormone can be repeated in a few hours. Usually improvement is dramatic. Rarely, a small amount of glucose is necessary to overcome the hypoglycemia which sometimes occurs among these individuals. As soon as the patient is able to retain fluids by mouth, the solution of sodium chloride and sodium citrate may be given orally, 1 or 2 liters daily. The patient should not be moved until treatment of the crisis has at least been started. After this treatment, hospitalization is advisable. If the journey to the hospital is of any great length, before starting the patient should receive intravenously 1,000 c.c. of a physiologic solution of sodium chloride and 0.5 per cent sodium citrate to which at least 10 c.c. of the hormone has been added.

THE CRISIS OF EXOPHTHALMIC GOITER

Most physicians are thoroughly familiar with the syndrome associated with exophthalmic goiter, when the disease is of sufficiently long standing for the characteristic symptoms and signs to appear. However, it is safe to assume that some clinicians have had little experience in the recognition or treatment of the crisis which sometimes occurs in this disease.

These crises may occur at any time in the course of the disease if the patient is not taking iodine. As a general rule, however, it is encountered in three groups of patients, namely:

* These patients are exceedingly sensitive to anything which places a sudden burden on their resources. I know of one patient who dropped dead while getting out of bed, and of others who died suddenly following minor surgical procedures, catharsis and similar comparatively trivial procedures.

(1) early in the course of the disease, among patients who have severe, fulminating, unrecognized exophthalmic goiter; (2) among patients under medical treatment who have been taking iodine, but suddenly discontinue such treatment; (3) following thyroidectomy, among patients who have exophthalmic goiter and who have not been given a sufficient amount of iodine preoperatively.*

Intense psychomotor stimulation and protracted vomiting are the chief characteristics of the crisis. In addition, the usual findings and symptoms of hyperthyroidism, together with the specific features of the syndrome of exophthalmic goiter, generally are present to some extent. However, the phenomena associated with the crisis may be so prominent that the ordinary and more diagnostic manifestations of exophthalmic goiter are overshadowed and may escape the notice of even experienced clinicians.

In the development of a crisis, loss of appetite and diarrhea frequently are the initial symptoms. These may persist for several days and may lead to a diagnosis of "intestinal flu." Patients in this condition, on the verge of crisis, often insist that they feel all right and that they are not sick. On examination, it is obvious that they are sick and have marked weakness and tremor. But they are usually pleasant, smile readily, and often are unconcerned. Among women, this mood may be replaced quickly by causeless weeping, especially if asked whether they have had crying spells. Some patients in this condition appear and act as though they were mentally dazed and they will have difficulty in comprehending what is told them or in following directions. Ultimately, vomiting usually occurs. Vomiting at first may be deceptive. Patients may not mention the fact that they have been vomiting and, as they do not appear nauseated, they may not be questioned specifically for this information. Occasionally, they may vomit, and immediately afterward may keep down a good meal.

*The thyroid storm which sometimes occurs immediately following thyroidectomy for hyperthyroidism regardless of the type of goiter should not be confused with the crisis of exophthalmic goiter. The severe postoperative reactions which sometimes occur after thyroidectomy among patients who have had adequate preoperative treatment with Lugol's solution bear only a superficial resemblance to the crisis of exophthalmic goiter.

Eventually, however, the vomiting is likely to become more protracted and, sometimes, it is so intense that nothing taken by mouth is retained. If this is the case, it is easy to make the erroneous diagnosis of pyloric obstruction, or even of pernicious vomiting of pregnancy. Occasionally jaundice also occurs. Usually this has the characteristics of the intrahepatic type of jaundice. It may vary in degree from that of a mere icteric tinge of the sclera to an intense jaundice comparable to that which occurs in obstruction of the common bile duct and it may be associated with abdominal pain.

As the crisis gains in momentum, the characteristic "stimulation" which is usually present in most patients who have exophthalmic goiter increases in severity. The restlessness and the "useless and purposeful" movements become intensified; it is almost impossible to keep the patient quiet. Such patients thrash around in bed and toss off the bedding. Almost invariably, the elbows become reddened from the continuous friction against the sheet. Ultimately, the psychic status may resemble that associated with acute mania, agitated delirium, or severe toxic psychosis. This intense agitation may persist until death or may give way to coma or severe prostration, in which case the patient is too weak to move. At this stage, the clinical picture is not unlike that of a "typhoid state" and, unless exophthalmos happens to be present, bears little or no resemblance to the symptoms usually thought to be associated with exophthalmic goiter.

Careful examination of the patient in crisis will usually disclose some evidence that suggests the presence of exophthalmic goiter. Almost invariably, there is tachycardia or high pulse pressure, or both. Intermittent or continuous auricular fibrillation is a frequent occurrence, especially among older patients. The various ocular signs, such as the stare, exophthalmos, or edema of the lids may be absent or so slight that they escape attention, although, in some instances, all of the classical ocular signs of exophthalmic goiter may be marked. If the thyroid gland is examined, almost always it will be firm and, at least, large enough to be palpated. Bruits and thrills at the superior pole of the thyroid gland are frequent. Enlargement of the thyroid gland frequently will not be visible. The skin, at first, is usually warm and moist but, as the loss

of fluid progresses, it becomes dry and dehydrated. Early in the crisis the oral temperature is normal; later, pyrexia, and ultimately hyperpyrexia, occur as the result of failure of the mechanisms of heat elimination or as a result of intercurrent infection, to which these patients are particularly liable to succumb.

Pathologic Physiology.—The pathologic physiology of exophthalmic goiter, either in the stage of chronicity or in that of crisis, still is understood imperfectly. The theory promulgated by H. S. Plummer remains as yet the most satisfactory. He felt that, as the result of an intense but unknown stimulation of the thyroid gland, an "abnormal" product was fabricated by the gland and was delivered to the tissues. He felt that this abnormal product possibly might be incompletely iodized thyroxin. Thus, the distinctive symptoms of exophthalmic goiter, and of the crisis, are the result of the reaction of this abnormal product on the organism, in contrast with the symptoms of "pure" hyperthyroidism as it occurs in association with adenomatous goiter with hyperthyroidism, or in association with hyperthyroidism induced by administration of desiccated thyroid.

In exophthalmic goiter, therefore, the total amounts of both products may be large or small and the relative amounts of each may vary. If there is an excess of the normal product and a relatively small amount of the inferior product, the clinical status of the patient approaches that observed among patients who have taken excessive amounts of desiccated thyroid or among patients suffering from adenomatous goiter associated with hyperthyroidism. Contrariwise, if the inferior product predominates in amount, the peculiar stigmas of exophthalmic goiter are the outstanding clinical phenomena. In such instances, the total amount of both products may be relatively small with the result that the patient has severe exophthalmic goiter and may be in a state of crisis although the metabolic rate is low.

Acting on this hypothesis, H. S. Plummer introduced the use of Lugol's solution in treatment of exophthalmic goiter. If the distinctive symptoms of exophthalmic goiter (in contrast with adenomatous goiter associated with hyperthyroidism) were the result of an incompletely iodized molecule of thy-

roxin, it was logical to suppose that these distinctive symptoms could be controlled by completely "iodizing" the abnormal molecule of thyroxin. In other words, by administration of iodine the abnormal product would be converted to a normal product and, simultaneously, the clinical status of the patient who had exophthalmic goiter would be converted to the clinical status of a patient who has "pure" hyperthyroidism, such as occurs, for example, following overdosage with desiccated thyroid.

The phenomena observed after administration of Lugol's solution to a patient who has exophthalmic goiter are, essentially, those postulated by the Plummer two-product hypothesis. The distinctive features of exophthalmic goiter, such as the stare, the "stimulation," and the symptoms associated with crisis are obliterated rapidly (generally in about five days). Exophthalmos, being largely an anatomical deformity, may remain. Those symptoms and signs which are primarily the result of an increased metabolic rate usually persist but, generally, are reduced in intensity.*

Diagnosis.—Diagnosis of the crisis of exophthalmic goiter usually is not difficult except among those patients who have severe exophthalmic goiter associated with minimal signs and symptoms. These cases may deceive even experienced clinicians. For example, intermittent auricular fibrillation, intermittent delirium, and profound prostration were the only significant features of one case. The clue to the diagnosis of this case was auricular fibrillation which could not be attributed to hypertension, mitral stenosis, or arteriosclerotic heart disease. In some instances, the diagnosis can be made only on the basis of the patient's response to therapy.

Laboratory studies furnish little assistance to diagnosis, which, in its final analysis, must be made at the bedside by purely clinical means. Here again, the prerequisite to making a diagnosis is keeping in mind the possibility of each of the various metabolic crises when a patient presents gastro-intestinal symptoms that do not conform to those seen in the usual run of intra-abdominal diseases.

* Decrease in the metabolic rate which usually, but not invariably, occurs after a patient who has exophthalmic goiter is treated with iodine, is a curious fact and one which was not anticipated by Plummer.

These patients usually are too ill and too restless to permit determination of the basal metabolic rate until after the crisis has been treated successfully. Then the basal metabolic rate generally will be found to be elevated, but in an appreciable number of instances, the degree of elevation will be surprisingly small. In uncomplicated cases, a leukopenia with a relative lymphocytosis will be found. This has little diagnostic value. The same applies to the concentration of blood urea which may be elevated.

Treatment.—The crisis of exophthalmic goiter may run its course, clear up spontaneously, and be followed by a period of gain in weight and relative improvement in the general condition of the patient as if a toxic product may have been eliminated. However, before the introduction of Lugol's solution the mortality rate at the clinic, among patients hospitalized because of crises, was in the neighborhood of 10 per cent. It is evident, therefore, that a patient in crisis is dangerously ill and should be so treated. Furthermore, there are few medical conditions which respond so quickly or so gratifyingly to treatment, as do the crises of exophthalmic goiter. Patients may appear almost moribund and, within several hours, seem well on the road to recovery. When properly treated, the disease carries a very low mortality rate. When institution of treatment is delayed too long, it may be impossible to prevent death. In this respect, the disease is comparable with diphtheria in which case early use of antitoxin is infinitely better than heroic treatment started too late.

At the clinic, the usual practice has been to treat the crises of exophthalmic goiter by repeated oral administration of Lugol's solution. Ten drops can be given every fifteen to thirty minutes in milk, grape juice, or water. If the patient vomits, the medicine again can be given immediately by mouth. The absorption of iodine takes place so rapidly that even though vomiting takes place almost immediately, some of the iodine is certain to be absorbed. Usually, after a few doses of Lugol's have been given, vomiting ceases, and then the interval between doses can be lengthened. In the first twenty-four hours 100 to 200 drops of Lugol's solution should be given. An additional 50 to 100 drops can be given daily for the next one or two days, after which the dose can be reduced to 10

drops three times daily. If the patient is comatose when seen for the first time, iodine can be introduced into the stomach through a tube.

Usually no additional treatment is necessary. Solutions of sodium chloride and glucose, given parenterally by any route, are of great value if the patient is severely dehydrated. Iodine, in the form of potassium iodide, also may be given intravenously; but this is rarely necessary. As a rule, sedatives are not indicated and, if given, usually fail to produce the desired effect. When the symptoms of crisis are alleviated these patients generally quiet down and sleep without artificial aid. Digitalis is contraindicated during the crisis and usually is not necessary afterwards. Ultimately, thyroidectomy is indicated in practically all cases. This should be delayed for at least three or four weeks or longer, during which time it is important to continue giving at least 30 drops of Lugol's solution daily. If the drug is discontinued, another crisis may develop.

PARATHYROID TETANY

The term "tetany" is used to denote a symptom complex which results either from increased alkalinity of the blood or from a decrease in the amount of physiologically active calcium dissolved in the plasma.

Normally there is about 10 mg. of calcium per 100 c.c. in the serum. About 3 to 5 mg. of this amount is united loosely with the serum proteins and is, therefore, chemically inactive. The remainder constitutes diffusible or chemically active calcium and, if its concentration is reduced, tetany may result. It follows, therefore, that, in the many diseases in which there is a reduction in the serum proteins and, consequently, a reduction of the total calcium, tetany does not occur because there has been no change in the concentration of the diffusible or chemically active calcium.

The alkalinity of the blood increases either as the result of administration of alkali or removal of acid radicals. Hence, tetany occurs from overbreathing (which removes carbon dioxide), from prolonged vomiting (which removes hydrochloric acid), or from poisoning from alkalis, notably sodium bicarbonate. The mechanism by which increased alkalinity of the

blood (decreased hydrogen ion concentration) produces tetany is not fully understood.

Most cases of **parathyroid tetany** occur among patients whose parathyroid glands have been injured inadvertently during the course of surgical procedures performed on the thyroid gland. True parathyroid tetany from any other cause is a medical curiosity. Tetany resulting from rickets, overdosage with alkalis, vomiting, and hyperventilation is encountered considerably more frequently. Irrespective of the cause, symptoms are essentially the same and can be relieved by the same measures. When the disorder is not the result of parathyroid insufficiency, treatment naturally should be directed toward removal of the fundamental cause. Tetany developing shortly after thyroidectomy increases the operative hazard materially and should be regarded as a major medical emergency. Although the individual seizures which occur among patients who have chronic parathyroid insufficiency rarely cause death,* nevertheless they may be exceedingly discomforting to the patient and alarming for the relatives to witness. Therefore, to that extent, they also constitute medical emergencies. The same remarks apply to the miscellaneous groups of conditions in which tetany is but one of the symptoms of the underlying disease, but, in such cases, the prognosis depends on the nature of the fundamental disturbance.

Pathologic Physiology of Parathyroid Tetany.—The excitability of nerve fibers and nerve centers is regulated by calcium and the metabolism of calcium is, in turn, regulated by parathyroid hormone. Absence of the parathyroid hormone causes a decrease in the serum calcium, from its normal level of 10 mg. to 7 mg. per 100 c.c. or lower. Coincidentally, irritability of nerve tissue increases. With the decrease in calcium, the inorganic phosphates of the serum are increased. This reciprocal relationship between the behavior of calcium and phosphates is the rule in most disturbances involving these ions. That is, as calcium decreases, phosphate increases and

* Laryngeal spasm terminating with asphyxia may occur in the dog following removal of the parathyroid bodies. Patients may experience fatal laryngeal spasm shortly after operations on the thyroid gland but, otherwise, it is infrequent, although nonfatal laryngeal spasm occurs with considerable frequency among patients suffering from chronic parathyroid tetany.

vice versa. Most authorities are of the opinion that the decrease in calcium rather than the increase in phosphate is responsible for the symptoms in tetany. It is true, however, that a solution of phosphate given intravenously produces tetany. Following such a procedure, however, the serum calcium diminishes.

Beyond the scope of this article are such problems as the fate of the calcium which disappears from the blood, the cause of the tetany associated with alkalosis and with hyperventilation, the possibility of a common denominator of parathyroid tetany and alkalosis, the various forms in which calcium is present in the blood, the relation of calcium to acid-base equilibrium, and the mode of action of the parathyroid hormone. However, it is necessary to point out that, because of its significance in therapy, absorption of calcium by the alimentary tract is always incomplete and that two-thirds to three-fourths of the ingested calcium is excreted in the feces. The amount absorbed is increased when the calcium is present in the bowel in a soluble form. Solubility and, consequently, absorption of calcium salts is favored by vitamin D and by acid intestinal contents and is interfered with by alkaline intestinal contents. Insoluble calcium salts are formed in the bowel in the presence of an excessive amount of phosphate and, thus, absorption of calcium is prevented.

Symptoms.—The unfolding of the clinical picture associated with parathyroid insufficiency can best be observed in man when it occurs accidentally following thyroidectomy. The initial symptoms usually consist of paresthesias, such as numbness and tingling, and sensations of stiffness in the lips, fingers, and toes. As the concentration of serum calcium declines further, the hands and the feet become cramped and, eventually, carpopedal spasm occurs. In these spasms, the wrist and elbow are flexed, the thumb is extended and adducted, the fingers are approximated, the interphalangeal joints are extended, and the metacarpophalangeal joints are flexed. The resulting deformity is roughly cone shaped and known as the "accoucheur's hand." Both hands are similarly affected. The feet and lower extremities may or may not take part in the spasm. These cramps are painful. Generally the thumb can be abducted against resistance but it promptly returns to its

original position. Stridor and crowing respirations frequently occur as the result of laryngeal spasm. Laryngeal spasm is a particularly serious symptom and demands immediate attention if it occurs in the early postoperative period. The vocal cords may appear fixed as though both laryngeal nerves had been injured. In fact, if both nerves have been injured, there is a good chance that the patient also has tetany as the result of injury of the parathyroids. Generalized convulsions rarely occur among adults as the result of parathyroid insufficiency, but occur much more frequently among children suffering from tetany from any cause.

Diagnosis.—Recognition of tetany usually is not difficult. In addition to the symptoms mentioned, two signs are of great value, namely, the signs of Chvostek and Trousseau. Chvostek's sign is elicited by lightly tapping the skin overlying the facial nerve. In tetany, a slight or marked spasm occurs in the muscles supplied by this nerve. This sign is not always pathognomonic for, sometimes, it occurs among essentially normal individuals. Trousseau's sign, although more inconvenient to elicit, is more reliable than Chvostek's sign. A blood pressure cuff is put around the arm and the pressure is raised and maintained midway between the systolic and diastolic blood pressures. If the test is positive, the accoucheur's hand, previously described, results. Pressure should be maintained for several minutes in doubtful cases. Both these signs occur regardless of the etiology of the tetany.

The diagnosis of parathyroid tetany can be established by chemical analysis of the blood. As already mentioned, the serum calcium is reduced usually to 7.0 mg. per 100 c.c. or lower, the inorganic serum phosphates are increased and even may exceed the calcium content. The serum proteins remain unchanged.

Occasionally hysteria simulates tetany, but in hysteria the clinical picture is bizarre or, at least, is atypical (for example, the carpopedal spasm may be unilateral) and the chemistry of the blood remains normal. In clinical practice, the hyperventilation that occurs in functional dyspnea probably accounts for more cases of tetany among adults than parathyroid insufficiency if tetany which occurs following thyroidectomy is excluded from consideration. Tetany caused by functional

dyspnea* can be relieved by placing a paper bag over the head and, thus, making the patient rebreathe carbon dioxide. But the patient will respond also to intravenous injections of calcium and, consequently, this response to therapy does not help much in diagnosis. In this type of tetany, the serum calcium and phosphates remain practically unchanged. In poisoning owing to soda bicarbonate, the carbon dioxide combining power of the blood is increased while the concentration of serum calcium and of phosphates remains normal.

Treatment.—From what has been said, the principles underlying treatment of acute parathyroid tetany are obvious. Calcium should be replaced in the serum and further loss prevented by injections of parathyroid extract. In actual practice, however, parathyroid extract is rarely necessary.

In critical cases, 10 per cent solution of calcium gluconate can be given intravenously, but, preferably, not until after blood has been withdrawn in order that the diagnosis may be established by chemical analysis. Calcium gluconate is available in ampules ready for intravenous injection. Ten c.c. of 10 per cent solution of calcium chloride also can be given; it is probably safer to dilute this with a solution of physiologic sodium chloride to make a solution of 0.5 per cent calcium chloride. Injection of parathyroid extract in doses of 10 to 100 units may be necessary in very rare instances but this should not replace calcium therapy. As soon as the patient is able to swallow, a heaping teaspoonful of calcium lactate dissolved in hot water can be given at intervals of one to two hours. At the clinic, powdered calcium lactate is preferred to the more expensive gluconate. Calcium salts in tablet form should not be given unless first they are dissolved completely in water. After the patient has been tided over the initial emergency (and he usually responds to treatment very rapidly), administration of calcium lactate by mouth should be continued at intervals of four to six hours throughout the day, until it can be determined whether or not the injury to the parathyroid glands has resulted in temporary or permanent tetany. This may require a few days or several weeks. In the

* A number of years ago tetany was encountered among patients suffering from the respiratory syndrome that sometimes followed lethargic encephalitis. Such cases are becoming increasingly less common.

meantime, calcium should be given often enough to control the symptoms. If solutions of calcium lactate are given frequently the use of parathyroid extract almost always is unnecessary.

In an appreciable number of cases, tetany will prove to be temporary. This can be determined by withdrawal of calcium; if the symptoms recur treatment should be resumed.

Treatment of chronic parathyroid insufficiency presents a number of problems peculiar to this condition, consideration of which is beyond the scope of the present article. The problems involved have been discussed by Boothby in detail and the merits of a diet low in content of phosphorus have been reported by Schelling and Goodman. In our hands, treatment has been facilitated by giving 10 drops of viosterol or its equivalent in cod liver oil daily.

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COMMON EMERGENCIES RESULTING FROM CONTACT WITH CERTAIN PHYSICAL AGENTS

EARL C. ELKINS

HEAT

TALBOTT pointed out that the deleterious effects of high external temperature have been known for perhaps 2,000 years. In Isaiah XLIX, 10, and Psalms CXXI, 6, there is caution against the danger of being smitten by the sun. In Jonah IV, 8, reference is made to a condition which was apparently heat stroke. The effects of high temperature were described in medical literature two centuries ago.

The effects of heat on the human organism are, of course, closely allied with meteorologic conditions, tropical climates, and endemic heat waves. The effects of heat are observed in connection with industrial occupations in which men must work in a high external temperature. Most of the literature written on the effects of heat seems to be concerned with reactions of the white race to sudden changes in external temperature.

A study by Shattuck and Hilferty³⁸ of sunstroke and allied conditions in the United States over a period of thirty years indicated that deaths attributable to excessive heat were distributed very irregularly. The mortality rate was much higher in urban than in rural communities. The mortality rates fluctuated markedly but there was a slight downward trend from year to year. These statistics indicated that the average mortality rate was relatively high in the first year of life, very low between the first and twentieth years of life, then gradually increasing to the age of seventy years, and increasing rapidly thereafter. The specific mortality rates among men and women less than twenty years of age and more than seventy years of age were about equal, but the mortality rate among men between the ages of twenty and seventy years was three times as great as among women of such ages. Probably this

could be correlated with occupation because the rate among women has increased with the increased employment of women. Shattuck and Hilferty stated further that, in the states which have a large colored population, the mortality rate among Negroes was 2.4 times greater than among the white population. Here again, correlation with occupation is suggested. Deaths were shown to occur in every month of the year which indicate that, in many instances, there was a relationship to industrial conditions rather than to climate. Nearly all the deaths, however, occurred in June, July, and August, the largest number occurring in July. This indicates the presence of a climatic factor.

Other physical agents entering into the effects of high external temperature are humidity and sunlight of short wave length (ultraviolet). Several authors^{34, 38, 41} suggest that the deleterious effects of sunlight are caused only by that of long wave length. Marsh,³¹ working with rabbits, was unable to produce sunstroke in a series of animals by exposing their shorn heads to the sun for long periods of time. He stated that the animals were uncomfortable only when the blood, heated by circulation through the hot skin of the head, elevated the temperature of the body to the level of heat stroke.

Likewise, the consensus among many authors^{9, 18, 34, 38} was that humidity did not play an important part in the effects of heat. However, McConnell and Yaglou²⁶ observed that men, working in still air that was at body temperature and was saturated with moisture, accomplished only a fourth of the work done in comfortable temperatures and humidities. Marsh³² pointed out that, at external temperatures of 90° F. (32.2° C.) with complete saturation of surrounding air, there was an uncontrollable rise in the temperature of the body. This rise occurred at the rate of about 4° F. per hour and the pulse increased at the rate of about 100 beats per minute per hour.²⁶ Also, much higher temperatures were withstood when the air was in motion than when it was still, provided that it did not reach saturation of humidity. Although humidity may not play a primary rôle in diseases caused by heat, it does play a secondary rôle in the production of these conditions, particularly in industry. Under normal conditions the body produces more heat than is necessary to maintain its temperature, the

excess being lost by conduction, convection, radiation, and evaporation. Conduction, convection, and radiation play a part only when the surrounding temperature is lower than that of the body. Evaporation plays the most important rôle in cooling the body and this can occur only when the humidity of the surrounding air is sufficiently low to allow evaporation to occur.^{31,40}

The physiologic resistance to high external temperatures depends on the proper functioning of the structures of the body, such as the circulatory system, the sweat glands (their innervation and blood supply), and the thermoregulating center. Considerable progress has been made in the study of diseases caused by high external temperature, but much remains unknown.

Many terms have been used to designate diseases caused by external heat but it is the opinion of most investigators that these diseases can be placed under three main headings, namely: heat cramps, heat stroke, and heat exhaustion.

HEAT CRAMPS

Definition.—Many descriptive terms have been applied to this particular condition, such as "miner's cramps," "stoker's cramps," "mill cramps," "cane cutter's cramps," and "fireman's cramps." All these terms are associated with the occupations rather than with the causative agent. "Heat cramps" seems to be the best term. This condition consists of painful spasms of the voluntary musculature following activity in a high external temperature.⁴⁰ It is the opinion of Talbott and others that the condition, heat cramps, is a clinical entity and is not a part of heat exhaustion or heat stroke.

Incidence.—Most cases of heat cramps occur in the summer months. Although there are no accurate statistical studies available, occurrence of heat cramps apparently depends on meteorologic conditions, type of occupation, and so forth. This condition seems to be endemic in certain centers.⁴⁰

Predisposing Causes.—Organic diseases and ill health increase the susceptibility of the individual to sudden changes in temperature. Alcohol lowers the resistance to high external temperature^{12,31,40} often, because the individual who has been on an alcoholic bout has not consumed the proper amount of

food and water to sustain a correct equilibrium between electrolytes at a time when he is exposed suddenly to excessively high temperatures. Inadequate intake of food also is a predisposing factor whether it be caused by upset of the gastrointestinal tract, or by anorexia from some simple cause.

Recent attacks of heat cramps not treated adequately render the patient susceptible to more severe attacks.⁴⁰ Most men who have mild cramps recover sufficiently at home, without specific treatment, so that they return to work the following day, only to succumb to a more severe attack of cramps at this later time.⁴⁰

Susceptibility to heat cramps suggests inadequate adaptation to hard work in an environment of high temperature. The phenomenon is generally evident during the first days of a heat wave, and the incidence of cramps is greatest before adaptation is complete.^{40, 41, 43}

It has been estimated that,^{7, 27, 37, 39, 41, 42} in a hot environment, workmen may lose as much as 7.5 liters of fluid and 22.5 gm. of sodium chloride during the working day.^{9, 12} Also, investigations have shown that, in cases of heat cramps, the concentration of sodium chloride in the blood serum is reduced 2 to 10 per cent, which is not associated with the other diseases caused by high external temperature. It seems reasonable to conclude that lowering of the concentration of the sodium and chloride ions in the serum, which results from loss of these substances through perspiration without being adequately replaced, is the principal mechanism in the production of heat cramps.⁴⁰

Clinical Findings.—The patient usually presents himself in a paroxysm of cramps, after work in a high external temperature. A description⁴⁰ by Welsh gave an accurate résumé of what usually is observed clinically. Welsh stated: "Gradual involuntary spasmodic contractions of certain groups of muscles occur. The flexors of the fingers as a rule are affected first. The cramps occur every few minutes. In other cases smaller muscles will remain unaffected and larger ones of the arms and legs or even ones of the abdominal wall develop the condition. Sometimes many muscles or groups are affected at one and the same time; at other times one muscle remains contracted from one to three minutes when it gradually re-

laxes. The beginning of the cramp is usually ushered in by a few feeble twitchings of the muscle about to be affected; these occur long enough before the general spasm for the patient to realize a cramp is coming. A cool breeze or a sudden jarring of the bed is often sufficient to throw the affected muscle into contraction. There seems to be a predilection for certain groups of muscles affected in the first attack to be the ones affected in the later attacks. In the well developed case, the cramps may occur every two or three minutes; later, they may occur at intervals of a half hour. The pain during the cramps seems to be severe. I have often had patients tell me that they would rather die than go through another attack. The pulse as a rule is normal but, in some cases, might be slightly accelerated, rarely being over 100. The skin often is clammy, sometimes dry. When perspiration becomes free the patient improves. The patient seldom vomits even though the abdominal muscles are involved."

The prodromal symptoms may be vague and, generally, they escape notice.⁴⁰ The attack may be preceded by mild vertigo, headache, feeble twitchings of the muscles and, occasionally, intestinal cramps.

Differential Diagnosis.—Heat stroke, heat exhaustion, and heat cramps arise in the same environment. However, it has been observed⁴⁰ that the duration of the heat wave before the onset of cramps is important, because heat cramps occurred the first two or three days; this was not true of heat exhaustion and heat stroke. Patients who have heat stroke have temperatures elevated to 108° or 110° F. (42° or 43.3° C.), but patients who have heat exhaustion have temperatures which are usually subnormal, and patients who have heat cramps have temperatures which are normal or slightly elevated. Heat stroke and heat exhaustion frequently are accompanied by delirium, convulsions, and coma, but the mental changes accompanying heat cramps are very slight.⁴⁰

Nocturnal cramps and cramps following exercise⁴⁰ are not distinguished easily, but any workman who has cramps during sleep should receive treatment for heat cramps.

In cases of heat cramps, gastric colic is bewildering, if other types of cramps do not exist. Otherwise, the diagnosis can be made without difficulty.

Prognosis.—Heat cramps subside quickly when the concentration of chlorides in the blood returns to normal. Recovery depends somewhat on the severity of the condition and on the means and rapidity with which the chlorides are restored.

Prevention.—Prophylactic measures include better working conditions, improved living conditions, rest periods, and suitable light clothing. The most important single measure is that of maintaining a proper amount of fluid in the blood and insuring an equilibrium between electrolytes by administration of sodium chloride in the drinking water. It is the consensus that, in industrial plants, or in places where men are working in an environment of high temperature, the most satisfactory method for supplying the proper amount of sodium and chloride ions is by using a solution of 0.1 to 0.5 per cent sodium chloride for drinking purposes.⁹

Treatment.—Treatment of heat cramps depends on replacement of sodium and chloride ions in the blood serum. This is considered a specific treatment.⁴⁰ In cases of severe cramps, intravenous injection of physiologic solution of sodium chloride should be performed immediately. Other methods of administering saline solution, such as by mouth or by hypodermoclysis, can be used. However, intravenous administration brings about recovery more quickly than administration by mouth and is much less painful than administration by hypodermoclysis. Cramps usually subside quickly after administration of sodium chloride. The patient then should remain quiet for twenty-four to forty-eight hours. Further replacement of the fluid and sodium and chloride ions should be accomplished by having the patient drink milk and other salt-containing fluids and eat foods which contain large amounts of salt.

Many empirical remedies have been used for heat cramps, but none are very satisfactory. Morphine is used frequently for severe cramps but, in many cases, it will not control the pain even when used in large doses.

HEAT STROKE

Heat stroke and heat exhaustion are not as well defined entities as heat cramps. Some investigators believe these conditions are a part of the same disease although they are asso-

ciated with different clinical pictures. Many terms have been used to describe the condition of hyperpyrexia caused by exposure to prolonged, extreme degrees of heat. Such terms are "sun traumatism," "solarism," "sun stroke," and "heat stroke." According to most investigators, these terms are synonymous, at least the actual clinical syndrome is the same in all.

Etiology.—The underlying mechanism of heat stroke is not known. Several theories exist concerning the etiologic factor. It has been suggested that it is caused by: (1) acidosis, (2) autointoxication as a result of the action of heat of the tissues of the body, (3) damage to the heat-regulating centers, or (4) exhaustion of the sweat glands.

Predisposing Causes.—The most important environmental factor is a uniformly high temperature over a relatively long period of time.¹³ Heat stroke is more prevalent among the very old, the very young, persons addicted to alcohol, and those who have had heat stroke^{12, 13} previously.

Prodromal Symptoms.—Hearne,¹⁸ in a study of 240 cases of heat stroke, stated that the most reliable premonitory signs were suppression of perspiration and increased urination.

Symptoms.—The symptoms are usually gradual in onset with dizziness, headaches, mental excitement, depression,¹² and frequent urination, but hyperpyrexia predominates. The skin is hot, dry, and flushed. The pulse is rapid; the blood pressure is elevated; the respirations are deep and labored.¹⁸ There may be pulmonary edema, loss of consciousness, delirium, coma, and death.¹⁸

Prevention.—The measures for prevention of heat stroke are similar to those for prevention of heat cramps. Hearne stated that heat stroke was absolutely preventable if the patient was treated immediately as a case of hyperpyrexia, as soon as he presented himself with a dry skin indicating suppression of perspiration.

Treatment.—The patient should be removed quickly to a cool place; as soon as possible, the body should be sprinkled or sponged with cool water and a fan should be directed on the patient's body until the temperature of the body is lowered to normal. Ice baths, packs, and ice enemas should never be used to reduce hyperpyrexia. The patient should be watched closely. Venipuncture should be done and 400 to 500 c.c. of

blood withdrawn if asphyxia occurs accompanied by cyanosis, distention of the veins, or pulmonary edema.¹² The patient should have prolonged rest in bed. He should avoid high external temperatures the rest of his life.

HEAT EXHAUSTION

Etiology.—The etiology of heat exhaustion is not known. It occurs after a prolonged exposure to a uniformly high temperature. It is believed to be caused by circulatory collapse, the exact mechanism of which is not known. It is thought that it may be caused by loss of fluids and chlorides, although many individuals who have heat exhaustion do not have a lowered concentration of chlorides in the blood. Frequently, the components of the blood are changed little from the normal.

Symptoms.—The patient is exhausted and has a pale, clammy skin. The blood pressure is low, the pulse is rapid, and the temperature is usually subnormal. The patient may be in a state of severe shock.

Treatment.—The treatment is mainly that of shock. The patient should be kept warm if his temperature is subnormal and care should be taken that the temperature does not rise quickly to dangerously high levels. Caffeine, epinephrine hydrochloride, and other cardiac stimulants can be used as indicated, as in any other type of shock. The most important single factor in the treatment of this condition is replacement of fluids, preferably by intravenous injection of physiologic solution of sodium chloride with or without 5 or 10 per cent dextrose.

FEVER THERAPY

The complications resulting from fever therapy are essentially those mentioned in this paper in the section, "Heat." It is to be emphasized, therefore, that artificial fever therapy administered by physical means should be done with the greatest care and under the control of a well trained personnel. The method of producing artificial fever (whether it is by a current of high frequency, aid-conditioned cabinet, radiant heat cabinet, or other physical means) probably makes little difference with respect to the possibilities of complications resulting

from use of an excessively high external temperature in such procedures.

The most frequent complications that occur while administering prolonged artificial fever are circulatory collapse, excessive hyperpyrexia, and burns of the skin. Circulatory collapse can be prevented largely by administering large quantities of 0.3 per cent saline solution by mouth, preferably 300 to 500 c.c. per hour of treatment. If fluid is not tolerated well by mouth, intravenous injection of 5 or 10 per cent dextrose in physiologic saline solution should be used. The blood pressure should be recorded frequently. With lowering of the blood pressure to a dangerous level (80 to 90 mm. of mercury, systolic), intravenous fluids should be administered freely.

Excessive hyperpyrexia is present if the temperature of the body becomes higher than 107° F. (41.7° C.). The patient should be removed immediately from the fever-producing device and the body cooled to the desired temperature. If the temperature does not decrease when the patient is removed from the apparatus, he should be sponged with tepid water and a fan should be allowed to blow directly on the body.

Adaptation of the patient to a high external temperature plays a definite rôle in administration of artificial fever by means of physical agents. If the patient is subjected to a prolonged treatment with fever therapy without preliminary preparation, there seems to be an inability of the peripheral vascular system to accommodate itself to the high external temperature that is required. Under these circumstances, cutaneous burns and general reactions occur more frequently than when the patient has had preparatory treatment. Therefore, preliminary treatment is given on the day preceding the long session of fever therapy to cause general peripheral vasodilation. The treatment should consist of either a short session of fever therapy, such as two or three hours at bodily temperatures of 101° to 103° F. (38.3° to 39.4° C.) or the patient should be immersed in a hot bath for thirty minutes, to elevate his temperature to 101° or 102° F. (38.3° or 38.8° C.). This is maintained for one and a half or two hours by packing the patient in blankets. Ultraviolet radiation has been used in conjunction with hot baths to cause further peripheral vasodilation. This is done by administering an erythema dose of

radiation. This is believed, by some, to be sufficient to allow accommodation of the peripheral circulation to the prolonged fever therapy that is to follow on the next day.

SENSITIVITY TO HEAT AND COLD

GENERAL CONSIDERATIONS

In recent years, sensitivity to heat and cold has been described. These conditions are not frequent, but they can present serious situations in certain instances.

Duke¹⁰ recently clarified, somewhat, questions regarding sensitivity to heat. He believed the condition was based on derangement of the heat-regulating mechanism and that the patient usually exhibited constitutional symptoms. Duke discussed the reflex-like reaction caused by heat and effort, on one hand, and by cold and effort on the other. He pointed out that the effort syndrome described by Lewis frequently is caused by sensitivity to heat or to cold. The patient gives a history of exhaustion, weakness, dizziness, fainting spells, a sense of fullness or oppression in the chest, palpitation, anorexia, and nausea.

According to work done by Horton, Brown, and Roth,²⁰ the local and systemic reactions of individuals sensitive to cold, were similar to those produced by injection of histamine or histamine-like substances. As a result of cold, it seemed that histamine was released and, in addition to producing the usual urticarial changes locally, sufficient concentration in the blood to cause a systemic effect at times was attained.

Symptoms of Sensitivity to Cold.—The local effects of sensitivity to cold are pallor during exposure, followed by redness, swelling, increased temperature on removal from a cold environment, urticarial eruption,^{10,20} sneezing, and swelling of the nasal mucous membranes.¹¹ After a latent period of a few minutes, systemic reactions develop consisting of flushing of the face, sharp fall in blood pressure, rise in pulse rate, headaches, dizziness, dyspnea, nausea, palpitation, syncope or a tendency toward syncope, and, when large areas are exposed there may be severe shock.²⁰

A large number of the patients studied by Horton, Brown, and Roth had systemic reactions resulting in syncope. A large percentage of these occurred while the individuals were swim-

ming and some of the episodes of fainting necessitated rescue of the individual. Thus, it can be seen readily that individuals exhibiting such a phenomenon could meet with a serious accident, especially while swimming.

Treatment of Sensitivity to Cold.—For immediate treatment, injection of epinephrine hydrochloride or immediate plunging of the arms into water at 42° C. (107.6° F.) will relieve the local lesions. Desensitization can be accomplished readily by having the patient take cold baths, gradually decreasing the temperature of the bath and increasing the period of immersion. Also, it may be accomplished by subcutaneous injection of histamine in gradually increasing doses.⁵

Treatment of Sensitivity to Heat.—This disease is less defined than sensitivity to cold. Duke¹⁰ thought the clinical symptoms were caused more often by defective response to change in temperature than to change in temperature itself. These patients are more comfortable in cool, dry climates than in warm, damp climates. Dryness seems to be the most important factor. More effort can be tolerated in dry atmospheres. Avoidance of very low bodily temperature is important. A febrile disease will often give relief, and subcutaneous injections of colon bacilli appear to be of value. Hot and cold baths may be very valuable.¹

FROSTBITE

Frostbite is a term loosely applied to superficial or deep lesions produced by exposure of portions of the body to extremely cold surroundings. There seems to be no close relationship between frostbite and humidity, but there is a definite relationship between frostbite and the velocity of the wind in cold surroundings.³ Brahdy³ found that external temperatures of 8° to 14° F. without a wind could be withstood without occurrence of frostbite, but a wind at this temperature caused the incidence of frostbite to rise to eight per 10,000.

Pathology.—Some authors^{8, 22} classify frostbite according to the depth of the lesion. The erythema of frostbite of first degree soon passes off as does that caused by superficial burn. Second degree frostbite is associated with blistering and, usually, regions of devitalized tissue will be found beneath the blisters which later become ulcers. Third degree frostbite is

caused by long exposure at a very low temperature; a whole extremity or part may be frozen solidly. This results in gangrene, ulceration, a line of demarcation, and, in severe cases, sloughing of the frozen parts.²²

At the onset of frostbite, constriction of the blood vessels occurs, which disappears when the part is warmed.³ In the more severe stages, the skin remains white, becoming purplish-black twenty-four to forty-eight hours later. In cases of mild frostbite, a few superficial cells are killed, resulting in a red, swollen, painful region which may remain for some time.² In moderately severe cases, necrosis of the epidermis and formation of blisters occur.² Most authors agree that gangrene of an extremity is caused either by prolonged contraction of the blood vessels or by formation of thrombi because of damage to the intima of the vessels.²² Experimentally, it has been shown¹⁶ that the content of protein in the blisters and the appearance of the lesions are very similar, pathologically, to burns or other like trauma. Histologically, chronic inflammation occurs in cases of frostbite. Examination of atrophic ulcers of the skin gives no evidence of a reparative process and all new tissue is much less vascular than usual.³ The pathologic and clinical picture of this condition is that of ischemia.³

Symptoms.—The patient complains first of tingling pain and numbness of the part. Later, as freezing occurs, all sensation disappears. As thawing takes place, the same symptoms that occurred during freezing are experienced but they are of greater intensity and the pain may be very severe.²²

Prevention.—Exposure to temperatures below 8° F. (or between 8° and 14° F. when there is a strong wind) should be interrupted frequently by short periods of rest in a warm atmosphere.³ It has been shown³ that the longer the individual remains in a cold environment, after he has experienced numbness and blanching of the skin, the more severe will be the degree of frostbite. Therefore, when such symptoms are experienced by individuals working in the cold, they should stop work for the day. Individuals working in a cold environment should have carefully fitted footwear and handwear. Often, individuals wear excessive amounts of clothes which may cause constriction of a part, thereby hindering circulation and en-

hancing the possibility of freezing. Individuals who have cardiovascular disease and diabetes should not work in a freezing environment.

Treatment.—No well proved treatment is known. The consensus among physicians and laity is that frostbite should be thawed slowly. If sudden thawing of frozen tissue occurs, severe pain, burning, and tingling result.²² It is stressed that rapid thawing may result in rapid development of inflammation of an exudative type accompanied by more damage than would be accounted for by freezing alone.²² However, in a series studied by Brahdý³ the rapidity with which frostbites were thawed made little difference. If there are open lesions, strict surgical cleanliness should be observed to prevent infection. Should blistering occur, surgical dressings should be applied. European authors have obtained good results by approximately vertical suspension of the frozen part during the period of thawing and for several days thereafter.²² They also have reported excellent results in treatment of acute frostbite by heated air. However, it has been stated recently that heat, massage, and other treatment usually used in treatment of vascular disease were not particularly satisfactory,⁴ the underlying factor apparently being more than vascular insufficiency. If gangrene occurs, treatment should be the same as for gangrene owing to any other cause.

ELECTRICITY

The wise use of electricity in industry and in households has made its dangers more obvious than previously, although accidents caused by electricity have not increased in proportion to the wide use of this powerful physical agent. In 1935, there were 630 deaths from electrical shock in the United States as compared to 6,228 deaths from drowning.⁶ It has been estimated that 0.5 to 0.9 per cent of all industrial accidents are caused by electricity.²⁸ The total number of accidents cannot be estimated accurately because many of these accidents are not reported. In one of the large electrical industries, it was found that only 7 per cent of all accidents were of an electrical nature, but the accidents caused by electricity were 160 times more incapacitating than those caused by mechanical trauma.¹⁷

FACTORS INVOLVED IN ELECTRICAL ACCIDENTS

Voltage.—Voltage neither determines the fatality, nor the extent of injury when the individual comes in contact with electrical current. Deaths have been reported from a current of 60 volts and recovery has been reported from shocks with 120,000 volts.⁶ Fatal accidents also have been reported from sinusoidal currents of 30 to 50 volts.¹⁵

Currents of low voltage (110 to 220 volts) used in homes and in industry have been considered erroneously as not dangerous, but the greatest number of deaths occur from currents that have voltages between 220 and 1,100 volts. The number of accidents caused by alternating current of low voltage seem to be increasing out of proportion to those caused by current of high tension.²⁵ High voltage has a tendency to throw the individual away from the contact.

Type of Current.—Alternating current of 39 to 150 cycles is most dangerous.²⁸ Currents of extremely high frequency, 400,000 and more, have no effect other than heating. It has been stated that, for man, alternating current is three times as dangerous as direct current. In one group of 212 fatal accidents, only eight were caused by direct current of less than 220 volts.²⁵ Laboratory experimentation has indicated that alternating current of 100 to 220 volts is more dangerous than a continuous current but, if the current was of 500 volts the dangers were more nearly equalized and, if the current was of 1,000 volts, continuous current was much more injurious than alternating current.²⁵ However, it has been established definitely that alternating current causes more severe burns than direct current.

Amperage.—Because amperage (intensity) is ascertained by dividing the voltage of the current by the resistance of the conductor, it is impossible to tell how much amperage can be withstood by the human organism.¹⁵ Experimentally it was found that 200 to 250 milliamperes of direct current, and 70 to 80 milliamperes of alternating current, respectively, proved most dangerous.²⁵ Seventy to 80 milliamperes are sufficient to cause death in man.¹⁵

Duration of Contact.—The duration of contact with electrical current is very important. The low voltage of the household current is not sufficiently strong to throw the individual

away, but causes vigorous contraction of muscles which tends to hold the individual in contact with the current. The better the contact the more dangerous the shock may be. Poor electrical contact may cause greater external damage, such as burning and charring, than good contact but the general effect is less. With good contact, there may not be much external evidence of burning, but the shock may cause a fatal result.²⁵ Electrical contact is enhanced by wet hands, perspiration, and light clothing; therefore, more electrical accidents occur during the summer.^{17,30} Likewise, any circumstance that insures better grounding of an individual, such as wet cement, or steel floors, is dangerous.¹⁷

Resistance and Susceptibility to Electric Shock.—Individuals who are aware of the dangers of shock can withstand shocks that would be fatal to individuals who are extremely afraid or who receive the shock unexpectedly.^{6,21} There is a definite difference in susceptibility to electrical shock between individuals. The general condition of the victim is a factor. Fatigue and hunger also are factors.

Resistance to passage of the current varies with the circumstances. The skin offers the most resistance, which varies from 3,000 ohms to 100,000 ohms depending on the site, thickness, cleanliness, and dryness¹⁵ of the skin. Sweat or moisture on the skin may reduce the resistance to 1,200 ohms which would allow passage of 92 milliamperes with a 110-volt current, which would be sufficient to cause death.¹⁵ This accounts for the dangers of electrical appliances in close proximity to the bathtub and the serious and fatal accidents that result from handling the ordinary household electrical current outlets, when the hands or body are wet because of perspiration or other reasons.

PHYSIOLOGIC AND PATHOLOGIC EFFECTS OF ELECTRICAL CURRENT

The exact mechanism by which electricity causes death is not known. The consensus is that death caused by an electrical current may occur from ventricular fibrillation, paralysis of the medullary centers, particularly the respiratory center, prolonged tetany of the respiratory musculature, and nerve block caused by passage of the current through the nervous system.^{17,25,28,35,36}

In the nervous system, petechial hemorrhages are found, particularly, in the medulla.²⁴ Chromatolysis occurs in the nerve cells. The cells are dark, the nuclei are shrunken and are often eccentric in position, and Nissl's bodies may disappear. Lesions of the peripheral nerves have been described as localized ballooning of the myelin sheaths. The myelin may disappear gradually, leaving vacuoles.²⁹ The axis cylinders may become fragmented.^{23,24} It has been stated that the electrical currents follow the great nerve trunks.³³ Laboratory experiments have indicated that the abnormalities produced in the central nervous system by direct current differ from those produced by alternating current. It was found that direct current caused more damage to the nerve cells than alternating current, although hemorrhage in the central nervous system was observed more frequently following contact with alternating current.²⁵

MacMahon²⁹ observed that, among animals, following electrical shock there was delayed vasoconstriction resulting from sympathetic stimulation which simulated the vascular phenomena observed in cases of "surgical shock," and which, in itself, would be sufficient to produce moderate ischemia, with the resulting deficiency of oxygen in the involved regions. Jellinek²⁸ stated that blood vessels became friable and brittle, that the endothelium was changed, and that parietal thrombi were attached to the intima.

When striated muscle comes in contact with electrical current tetanic contractions occur, the spasm being so intense as to cause rupture of the muscle, luxation of the joints, and fracture of the bones of the part.²⁵

Lesions of bone are reported to occur frequently when the current enters the body through the skull.²¹

Constant lesions are not found in the large organs of the body. Frequently no abnormalities are found.^{24,29} Among experimental animals, search for microscopic findings was disappointing except in the central nervous system.²⁹ Congestion of the heart, spleen, kidneys, and peripheral lobules of the liver, and congestion and petechial hemorrhages of the lung were observed. No constant lesion was present in the heart.²⁹

Electrical Burns.—The electrical burn is characteristic. It may have an appearance varying from that of a small punc-

ture wound to that of complete charring of a part. Electrical burns of first and second degree may simulate any other type of burn, but electrical burns of third degree are pathognomonic. The center usually has a charred appearance; immediately outside this, there is a blanched, pale, yellowish-white region and, surrounding this, there is a narrow reddened line of hyperemia.^{24, 33} The cells of the outer layer of the epidermis are pressed together closely, as if by mechanical means. The cells of the rete malpighii and their nuclei are elongated to five or six times their usual length and the papillae are flattened.¹⁷ There appears to be a molecular change in the cells which goes on to cellular and molecular death.¹⁷ If a strong electrical current enters by the hand and leaves by the foot or if the current enters and leaves the same extremity, the part may become completely gangrenous.

Symptoms following Electrical Shock.—Immediate effects may vary from the slightest tingle to sudden death. There may be rigidity or tetanic contractions of the muscles, local or generalized, depending on the intensity and the pathway of the current. If muscular spasms are sufficiently prolonged, they may cause asphyxiation and death. Unconsciousness or peculiar sensory disturbances occur in most instances, following which there is a feeling of exhaustion, tension in the muscles, and headache. Pain is usually present. It may be generalized and agonizing following shocks from high voltage. Tinnitus and deafness often occur temporarily; also, disorders of vision are frequent. Restlessness, irritability, and maniacal excitement may occur in the period of unconsciousness. The period of unconsciousness may be short or may last for several days following which there may be a period of amnesia. The pulse is hard and tense. Micturition and defecation may be inhibited. Acute pulmonary and cerebral edemas are not infrequent.^{17, 24, 28}

The secondary and late effects of electrical shock may be paralysis, hemiplegia, and paraplegia. There may be signs of abnormal function of the autonomic system resulting in edema, cyanosis, peripheral arterial spasm, and Horner's syndrome. There may be disorder of speech which disappears in a few days. Auditory or vestibular damage has occurred. Typical pictures of disseminated sclerosis have been produced by elec

trical shock. Clinical pictures resembling progressive muscular atrophy or amyotrophic sclerosis have been described as appearing after an interval of a few days or a few months.²⁴

Treatment of Electrical Accidents.—Prevention of electrical accidents must be accomplished through education and measures for safety in industry and by enlightening the general public and emphasizing the hidden dangers that lie in the prevalent source of power that surrounds it.

The most important treatment of electrical shock is artificial respiration. This should be done immediately after the patient is removed from contact with the electrical current and should be continued until the patient continues to breathe naturally or until all evidence of life has disappeared. The criteria for death of such an individual differ from those in other cases, because there may be no reflex reactions whatever. The patient should not be pronounced dead until rigor mortis sets in, or until cooling of the body occurs. It has been recommended that artificial respiration be administered for three to eight hours.

The method of resuscitation preferred in this country is the Schaefer method which is performed as follows: The patient should be lying on his abdomen, one arm extended beside the head, the other bent at the elbow with the face turned to one side and resting on the hand or forearm, so that the nose and mouth are free of obstruction. The operator then straddles the patient's hips, his knees just below the patient's hips. He then places the palms of his hands on the small part of the patient's back with the fingers extended over the ribs, the little finger just touching the lowest rib, the thumb beside the fingers, and the tips of the fingers just out of sight of the operator. The operator then slowly counts one, two, and with straightened arms swings slowly forward, so that the weight of his body is gradually, but not violently, brought to bear through the arms and hands on the patient. This act should take from two to three seconds. Then, counting three, the operator swings backward, removing the pressure; he then counts four, five, as a rest period. These maneuvers, swinging forward and backward, are performed twelve to fifteen times a minute, causing complete respiration every four or five seconds. Artificial respiration should be continued without inter-

ruption for any reason until death is assured definitely or until the patient breathes naturally. If natural breathing ceases after being restored, artificial respiration should be started again immediately. Because there is great shock to the individual, emotionally as well as physically, and also because there are latent effects resulting from strong electrical shock, the patient should be kept at rest in bed for two or three weeks, in severe cases.

Treatment of Electrical Burns.—The consensus is that electrical burns should be treated as any other burns¹⁴ are treated. Hemorrhage very rarely occurs immediately following electrical burns but secondary hemorrhage frequently follows after shock has been controlled and after arterial blood pressure rises. Damage to the blood vessels in the immediate vicinity of the burned region usually is not widespread in the arteries, but damage may extend for some distance in the veins. All electrical burns should be treated as serious conditions, no matter how trivial they may seem. In cases of extensive burns, early application of tannic acid is advocated.¹⁴ Most authors recommend avoidance of early surgical intervention. On the other hand, it has been suggested that immediate débridement or excision of the burned region beyond the hyperemic margin and suturing should be done.³³ Débridement of tissue well beyond the scar should be performed to insure inclusion of damaged vessels. This method is believed to lessen the disability resulting from extensive burns.

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DIFFERENTIAL DIAGNOSIS OF ABDOMINAL PAIN

ALEX E. BROWN

PAIN is of tremendous importance to the patient. It also often constitutes a key whereby the physician can disclose the secret of many disorders. Of course it is always necessary to consider this symptom together with other fundamental data, but study of the pain syndrome alone often affords a valuable clue in diagnosis. Care must be taken to adjust interpretation of pain according to the individual's threshold of perception of pain. Certain sensitive individuals possess an irritability which permits mild stimuli to produce a profound sense of pain whereas the severe pain of a gangrenous appendix will at times cause individuals of a phlegmatic temperament little more than discomfort. These differences are of course dependent on familial traits as well as on racial attributes. Environment is also a vital factor in encouraging or discouraging resistance to hardship and suffering.

CONCEPTS OF PAIN

Before effective thinking on, and logical analysis of, the pain syndrome can ensue it is necessary to have some basic anatomicophysiologic concept of the production of abdominal pain. The early ideas of Lennander and those of Ross, together with modifications which have followed from the studies of McKenzie, Head, and others of more recent date, all have contributed to knowledge of this subject, and although any one physician may personally adhere more closely to one hypothesis than to another, it is necessary to realize that all afford a certain basic background for interpretation of pain. Although much remains unexplained, and some criticism may be leveled at each hypothesis, one apparent rational approach to the problem seems afforded by the views of Morley. He affirmed

the existence of two fundamental types of abdominal pain: one derives from the autonomic nervous system and the other from the somatic or cerebrospinal nervous system. The first of these, splanchnic or visceral pain, according to Morley, results from stimulation of the afferent splanchnic nerves which, according to his belief, afford the principal nerve supply to the gastro-intestinal tract, gallbladder and liver, uterus and fallopian tubes. He expressed the belief that somatic or parietal pain results from stimulation of the afferent somatic nerves which supply the parietal peritoneum and sensitive mesenteric regions. Although undoubtedly both nervous systems are connected with the thalamus, it seems likely that somatic pain, with its clearer definition, is also connected with the sensory cerebral cortex.

Visceral pain thus appears to be the more obscure in nature and to lack precise localization. It is likely to be dull and heavy in character, is usually deep-seated and, in addition, is often spasmodic and intermittent. Somatic pain is sharp and stabbing in quality and usually is superficial and continuous in nature. It is associated with tenderness and rigidity of the abdominal wall and these phenomena are characteristically present at the site where the patient perceives the pain. Splanchnic pain is the result of abnormal tension on splanchnic afferent nerve endings in the muscular walls of hollow viscera. A classic example is encountered in early intestinal obstruction of which the pain may remain unlocalized and tenderness or rigidity of the abdominal wall may be absent. Somatic pain presents the familiar picture which is seen in association with inflammatory lesions, which, when the parietal peritoneum is involved, present an area of localization with tenderness and rigidity. Morley has cited pain at the tip of the shoulder which results from irritation of the phrenic nerve to the diaphragm as affording a classic example of somatic pain which is referred in a characteristic manner to the cutaneous areas of the shoulder that are supplied by nerves which arise from the third and fourth cervical segments. In a similar way, abdominal pain in general is referred by way of each of the lower six thoracic and the first lumbar nerves to a strip of parietal peritoneum and an overlying strip of musculature and skin. In general, it seems likely that this segmental

distribution, as Burgess has pointed out, tends to cause pain to be referred from the stomach to the area between the xiphoid process and the umbilicus, that from the duodenum to the area close above the umbilicus and that from the large intestine to the midhypogastric line. Pain from the liver, gall-bladder, and bile ducts frequently tends to be referred to the lower part of the epigastrium.

Certain pain syndromes, however, such as the visceral pain of gastric and of duodenal ulcer, are more difficult to explain and it is possible that they may be dependent on some conditioned heightening of sensitivity to chemical changes, to vascular congestion or to other factors.

Fundamentally then, with some explanation such as the foregoing in mind, the physician is aided in distinguishing between lesions which produce only distention of a hollow viscus, with exaggerated peristalsis, and those which produce true parietal peritoneal irritation.

GENERAL APPROACH TO DIAGNOSIS BASED ON PAIN

In the general approach to the problem of differential diagnosis of abdominal pain the development of an exacting history is of primary importance and it is of course necessary to delve into all previous relating factors which could have a bearing on the case in question.

The family history may throw light, as previously has been mentioned, on the sensitivity of an individual to pain. In the case of the individual of forty or more years of age, a family history of arteriosclerotic heart disease may indicate the possibility of abdominal pain secondary to atypical angina pectoris or coronary thrombosis. The predominance of a familial tendency to cancer should cause one to consider malignancy as a cause of obscure abdominal pain.

The history of past illnesses must be carefully elicited, inasmuch as they may have considerable relationship to the presenting problem. One classic example of this relationship exists in the syndrome of disease of the gallbladder which may have had its origin in an attack of typhoid fever years previously. Another is furnished by the history of previous infection with *Endamoeba histolytica*. In the latter instance valuable information may be offered by the history of exposure,

of diarrhea or of the extent of treatment. A history of tuberculosis may offer an explanation for the puzzling picture which proves to be attributable to tuberculous peritonitis. Similarly, a history of tuberculosis or trauma may serve as a clue to discovery of the etiology of a lesion of the back with referred abdominal pain. Pain of this type is not uncommon and care in developing the history frequently will throw light on the true nature of the condition. The menstrual or marital history of the female may throw light on various pains associated with the menstrual cycle, marital relations or complications of childbirth.

The problem of rapidly and accurately obtaining the history of the present illness is of importance. It will be aided by: first, estimating the severity of the pain from the action and facies of the patient and, second, by having the patient definitely locate the pain, not in generalities but by specific pointing with the finger. In the acute case, however, the previous administration of a narcotic may cast considerable confusion on these issues. With these preliminary data in hand, further question may be made as to the mode of onset and duration of the disorder. The history of previous similar attacks is important in bringing to mind recurrent fulminant disorders associated with the gallbladder, gastro-intestinal tract or kidneys.

If previous similar attacks have occurred inquiry should be made as to antecedent factors affecting the pain. Has the taking of food resulted in distress, has distress been affected by the act of defecation or micturition, has it resulted from bodily motion or even from changes in weather? Answers to these questions may serve to direct further attention to the gastro-intestinal, genito-urinary or musculoskeletal systems.

Next the extension of the pain must be ascertained and this may give a most important clue to the disorder. Extension of pain from the posterior lumbar region, anteriorly to the bladder or genitalia, suggests the presence of renal stone, hydronephrosis, renal tumor or other condition of the kidney while a similar extension, from the anterior lumbar region, may suggest the presence of a ureteral calculus. Extension of upper abdominal pain, around the subcostal region to the right scapular area, of course suggests disease of the gallbladder, al-

though rarely this pain may be present in the left epigastrium and extend to the left. Pain which is projected straight through to the back suggests a perforated peptic ulcer, if it is severe, and may be owing to a penetrating type of ulcer if less severe. The presence of deep, boring epigastric pain extending through to the back may also suggest the presence of a lesion of the pancreas or bile duct. Pain which extends anteriorly from the spinal column, particularly when there is a tendency for the pain to be projected to the hips or thighs, frequently bespeaks the presence of a spinal lesion.

CONDITIONS WHICH MAY CAUSE ABDOMINAL PAIN

In considering the actual individual lesions which may contribute to abdominal pain, the subject is seen to be so vast that it is possible only to touch on some of the outstanding points of interest. The subject may be classified as to specific organs involved, topographical distribution of lesions, degree and type of pain and so forth. For the present purpose, however, it would seem best to discuss certain of the important pain syndromes, together with the various similar conditions which may occur in associated abdominal regions.

Pain Referred from Outside the Abdominal Cavity.—

First, I think it advisable to discuss briefly those conditions which produce abdominal pain through reference from regions outside the abdomen. One group of these conditions is composed of those which cause back-pain, particularly when low thoracic in situation. In this instance diagnosis will be aided by the history of origin of the pain, by knowledge of its extension and by its relation to posture, motion and thermal variations. Pneumonia and associated pleurisy frequently produce abdominal pain which is distinguished with difficulty from that produced by acute intra-abdominal lesions. The height of the temperature, the presence of symptoms referable to the upper respiratory tract and the occurrence of dyspnea may suggest that pneumonia or pleurisy is present and confirmation can be obtained by general or roentgenologic examination of the thorax. Angina pectoris may give rise to chronic, intermittent epigastric distress and the symptoms of coronary occlusion may resemble an acute abdominal episode. The former condition occurs not infrequently among individuals such as farm-

ers, who, in the press of work, may perform chores immediately after meals and thus cause the development of a postprandial syndrome of pain simulating peptic ulcer. Careful elicitation of the history will disclose details of an exertion-pain, rest-relief syndrome, and frequently will disclose the relationship of pain to exercise after heavy meals or to walking into a cold wind. In a case of coronary thrombosis, the history of previous anginal attacks, when present, and the picture of a patient in a state of cardiac collapse, who complains of pain or pressure in the chest, together with a lack of clear-cut abdominal findings, usually will serve to create a suspicion which can be confirmed by the electrocardiograph.

Visceral Crises.—The various “visceral crises” associated with migraine, syphilis, tumor of the fourth ventricle or encephalitis also may closely simulate the pain of organic abdominal disease. Migraine, particularly when headache is absent or plays a minor rôle in the syndrome, may closely resemble the symptoms of a disorder such as disease of the gallbladder. Careful detailing of a history of the relationship of recurring attacks to nervous strain and fatigue, rather than to characteristic dietary indiscretions, will be of importance. Of value also is the absence of clear-cut abdominal findings such as tenderness and rigidity proportionate to the general stormy picture which is presented. This absence of localizing abdominal findings is of value also in detecting the “gastric crisis” of syphilis, and the diagnosis of course may be aided by the history of the development of syphilis and the presence of confirmatory stigmas of its presence. In this connection, the physician must be on the lookout, also, for the presence of organic abdominal lesions of syphilis which may produce more chronic symptoms of varying types.

Poisoning and Allergy.—In making a diagnosis, care also must be taken not to forget the possibility of poisoning by foods or chemicals and of food allergy. In the condition first named, the history of a dietary indiscretion and the chronologic association of nausea, vomiting and diarrhea, together with the absence of rigidity or increasing tenderness, is important. Similarly, chemical poisoning such as that resulting from lead or arsenic may cause generalized abdominal distress; the acute pain of plumbism may be confused with that

attributable to other lesions. A diagnosis of plumbism may be entertained when an organic lesion is not found to account for the pain, when a lead line is present on the gums, when basophilic stippling is discovered in the blood smear or when lead is found in the urine.

Sensitivity to food or food allergy at times can produce pain which closely simulates that of organic abdominal lesions and of gallbladder disease in particular. It is particularly necessary to consider these nonorganic conditions when the presenting symptoms are not characteristic of organic disease and laboratory procedures fail to confirm the presence of such disease. Aids to the correct diagnosis are a history of previous urticaria or angioneurotic edema, possibly the obtaining of relief by administration of epinephrine and determination of the absence of leukocytosis or of localized tenderness.

Appendicitis.—In considering the individual abdominal entities which produce pain, first place must be given to appendicitis, a condition which may be confused with almost any other acute disorder of the abdomen. The pain syndrome is of paramount importance in making this diagnosis. The pain of acute appendicitis is characterized by an onset which masquerades as diffuse soreness, usually present in the mid-epigastrium. This pain is situated deeply and indefinitely. It increases in severity and frequently assumes the nature of colic; then, after three to five hours, it becomes localized in the right lower quadrant of the abdomen. It is usually not situated deep in the pelvis but is usually lower than the pain seen in other conditions of the right side of the abdomen, with the exception of those originating in the pelvis. This early pain of appendicitis is definitely of a splanchnic or visceral nature, and when involvement of the right lower quadrant occurs there is tenderness and rigidity such as is associated with somatic pain. A characteristic accompaniment of the pain is the presence of nausea and vomiting. It is to be emphasized, however, that leukocytosis, fever, or nausea and vomiting may be absent but the presence of the characteristic pain syndrome, in the absence of any other suitable explanation, is sufficient to justify exploration.

Just as appendicitis, when associated with peritonitis, may resemble other acute abdominal disorders, so also may many

of these disorders similarly suggest appendicitis. Particularly confusing are certain manifestations of disease of the urinary tract, such as calculus, hydronephrosis, tumor, pyelitis or perinephritic abscess. Of importance in differential diagnosis, by which these conditions can be excluded, is the presence of past history of characteristic attacks of appendicitis, absence of pain in regions into which renal pain usually extends, lack of urinary symptoms and negative urinalysis. True chills, although common accompaniments of inflammation of the urinary tract are rare in association with appendicitis. It must be emphasized at this point that when appendicitis is suspected, or when chronic abdominal disorders in general are present, but symptoms cannot be satisfactorily explained, attention must be given the urinary tract and recourse may be had to cystoscopic examination or pyelograms if necessary. In this regard, Braasch pointed out in 1920 that in his experience fully half of the patients who came to him with lesions of the right kidney and ureter had undergone previous operations on adjacent organs, while the condition of the ureter and kidney remained unrecognized. Bumpus and Thompson also, in a study of 1,001 cases of ureteral stone, pointed out that the symptoms were suggestive enough to lead to appendectomy in 22.6 per cent of cases.

Prone to be confused with appendicitis also are various gynecologic conditions, particularly gonorrheal salpingitis, ectopic pregnancy and ovarian cyst. Of importance in reaching the decision that these conditions are not causing the symptoms is the presence of a normal menstrual cycle. Evidence against salpingitis is lack of history of exposure to gonorrhea, failure of the examiner to find evidence of vaginal irritation or to find *Neisseria gonorrhœæ* and lack of characteristic bilateral masses or tenderness of the tubes. Ruptured ectopic pregnancy usually is characterized by sudden, severe pain in the lower part of the abdomen, normal or subnormal temperature, the evidence of hemorrhage that is presented by pallor or air hunger and rapid, thready pulse. Usually, when ectopic pregnancy has taken place, a boggy mass can be detected in the cul-de-sac of Douglas and pain frequently accompanies a bowel movement. A twisted ovarian cyst on the right side may present an extremely difficult diagnostic problem but, at

onset, the pain usually is in the pelvis, and tenderness, without rigidity, may be present for a considerable time; palpation often will reveal the presence of an inflammatory mass and manipulation of the uterus usually accentuates the pain.

Appendicitis also must be distinguished from disease of the gallbladder and from such conditions as malignancy of the cecum, slow perforation of a peptic ulcer and strangulated inguinal or femoral hernia. Characteristic evidence of each of these conditions frequently can be obtained from the history or physical examination. Regional ileitis involving the terminal part of the ileum may be suspected because of continued intermittent attacks of pain and obstruction and the diagnosis can be confirmed by roentgenoscopic examination. Similarly, a tumor of the small intestine may produce intermittent attacks of pain, owing to partial obstruction. An inflamed Meckel's diverticulum also may exist and be diagnosed only at operation.

Chronic appendicitis is a diagnosis which must be applied with caution in the presence of vague abdominal conditions; the diagnosis frequently leads to difficulties. The condition occupies a position of much less prominence than the one it formerly held but it must be judiciously considered and possibly could best be termed "recurrent appendicitis." The diagnosis must be entertained when the patient presents himself with persistent or recurring pain in the right lower abdominal quadrant and a history of a previous attack of acute appendicitis, or when the patient is seen in one of a series of recurring attacks of pain in the right lower quadrant, with definite signs of appendiceal involvement, such as some tenderness and rigidity.

Peptic Ulcer.—In the upper part of the abdomen, mild to moderate chronic pain occurs, principally in association with ulcer or disease of the gallbladder. The diagnosis of peptic ulcer is easy when the symptoms occur with chronicity, periodicity, and regularity. It is further simplified when the syndrome is characterized by pain at night and by relief after the taking of food or soda or after emesis. Final confirmation of the diagnosis is, of course, dependent on roentgenologic findings.

The pain of peptic ulcer must be distinguished from that

of several other conditions. The mild to moderate pain of disease of the gallbladder is characterized by its chronicity and irregularity. In this condition, definite relationship to food usually is lacking unless the food is heavy, rich or greasy but belching, gaseous distress and a feeling of abdominal fullness frequently are present. Gastric carcinoma may account for chronic upper abdominal distress and may be characterized by long difficulty typical of that of ulcer; by intermittent symptoms of long duration succeeded by more recent, continuous distress, or by a nondescript group of upper abdominal symptoms of comparatively recent occurrence. The latter group of symptoms may also herald the presence of gastric syphilis, which can be diagnosed only by exhaustive study. Pain somewhat similar to that of peptic ulcer occasionally may be presented by diaphragmatic hernia and in this instance a history of previous trauma may lead to a suspicion of the diagnosis. In the presence of rather definite symptoms of an active gastric ulcer it may be well, when the roentgenologic findings are negative, to suspect gastritis and to resort to gastroscopic examination. The pain of gastritis frequently is accentuated by stooping forward, as Eusterman has pointed out. Symptoms of renal lesions, such as have been mentioned, are particularly likely to simulate those of peptic ulcer and should be investigated if the impression that a gastro-intestinal lesion is present cannot be substantiated. Epigastric hernia may serve to produce a group of ulcer-like symptoms consisting of indefinite, cramp-like pain or pain definitely localized at the site of the hernia. Subacute or chronic pancreatitis often is associated with disease of the stomach or gallbladder and may also give rise to upper abdominal pain which has a tendency to appear two or three hours after meals. It may be characterized by pain in the left epigastrium referred to the back, and by a half-girdle zone of hyperalgesia.

When surgical operation has been performed for a duodenal ulcer, appearance of the former pain usually indicates return of the ulcer. When gastro-enterostomy has been performed, and the pain is below, and extends somewhat to the left of the former site, a gastrojejunal ulcer is to be suspected.

Pancreatitis.—Probably the most severe pain in the upper part of the abdomen occurs with the presence of acute hemor-

rhagic pancreatitis, although that produced by a perforated duodenal ulcer or that of gallbladder colic may be equally severe. Pain is a symptom of paramount importance in the diagnosis of acute pancreatitis. It occurs suddenly and violently and, according to Moynihan, "of all the pains the human body can suffer, this is by far the worst." Morphine as a rule gives little relief in ordinary doses. It must be remembered that 65 per cent of the patients are females, and that associated disease of the gallbladder is present in 71 per cent of cases, often with an antecedent history. Severe pain in the left side of the abdomen, to which V. Katsch has called attention, when present with tenderness of the left hypochondrium, appears to be pathognomonic of the condition. Vomiting quickly becomes associated with the pain and some degree of shock soon follows. Cyanosis may also be present. Tenderness and rigidity are both present and are especially marked in the epigastrium; they are not as marked, as a rule, as when they occur with a perforated duodenal ulcer. It already has been pointed out that 65 per cent of the patients who have acute pancreatitis are females; even a larger incidence of those who have perforated duodenal ulcer are males.

In distinguishing pancreatitis from acute appendicitis with general peritonitis, it must be remembered that even when diffuse rigidity is present in the latter condition, the area of greatest rigidity is likely to be that which lies over the appendix. Also, in acute appendicitis with general peritonitis, rectal palpation may reveal tenderness or a mass, just as with a twisted ovarian cyst or ectopic pregnancy the pelvic findings will predominate. It is rare to elicit positive findings on rectal or vaginal palpation in association with acute disorders of the upper part of the abdomen. The picture, pancreatitis, is likely to be confused, also, with acute intestinal obstruction but only when strangulation and associated tenderness are present. In the latter condition, detection with the stethoscope of borborygmus occurring at the height of intermittent colic usually will serve to establish the diagnosis.

Disease of the Gallbladder.—The various diseases of the gallbladder play a prominent rôle in causing upper abdominal pain and the classic syndrome of right subcostal pain referred to the right scapular region is, of course, diagnostic. It must

be remembered, in this regard, that when a stone is present in the common bile duct, in association with jaundice, classic colic occurs in 60 to 70 per cent of cases, atypical pain in 20 to 25 per cent and pain is absent in 6 per cent. If pain recurs after cholecystectomy, benign stricture of bile ducts must be considered. When the condition is benign stricture of the common or hepatic ducts the pain usually is less severe than that present before operation and may be more in the nature of dull abdominal soreness. Colic, however, occurs in about 30 per cent of cases of benign stricture. When postcholecystectomy pain is present, and the question exists whether it is attributable to recurrent stone of the common duct or to benign stricture of the duct, it is important to recall that the symptoms of stricture usually come soon after operation whereas in cases of recurrent stone there is usually a lapse of about four years.

In considering the pain of obstructive jaundice it is well to remember that this is largely dependent on the rapidity with which, and the degree to which, the bile ducts are occluded. Hence, colic may occur in association with pancreatic obstruction attributable to malignancy just as, on the contrary, a stone in the common duct may fail to produce colic. Thus, about 25 per cent of patients who have a carcinoma of the head of the pancreas have colic while about 40 per cent of such patients do not have pain. When the malignancy involves the bile ducts there will be deep-seated pain in about 66 per cent of cases.

Carcinoma of the gallbladder, although of rare occurrence, may be suspected in certain instances if there is a history of cholecystitis of long standing, if the patient is an elderly woman and if there is a persistent right subcostal pain associated with loss of weight and weakness. Finding of a palpable mass in the gallbladder area tends to substantiate the diagnosis.

Conditions of the Left Lower Quadrant.—In considering pain situated in the left lower quadrant of the abdomen, the physician again must include in differential diagnosis the various renal and pelvic conditions previously cited. As appendicitis is characteristically accompanied by pain in the right lower abdominal quadrant, so also are diverticulitis and carcin-

oma of the sigmoid likely to be associated with pain in the left lower quadrant. Both may give rise to chronic, dull aching and, if perforation occurs, the symptoms and signs of true somatic irritation are found; namely, localized pain, tenderness and rigidity. A history of loss of weight, diarrhea or hemorrhage may aid in diagnosing carcinoma, whereas the patient who has diverticulitis may give a history of constipation associated with the occurrence of previous acute attacks of pain, tenderness and so forth, in the left lower quadrant. Frequently, also, in a case of diverticulitis previous roentgenologic examination of the colon will have revealed the presence of diverticulosis. The pain of an enlarged spleen may give a dragging sensation in the left portion of the abdomen but palpation of this organ will clarify the diagnosis.

Pelvic Conditions.—True pelvic pain usually can be attributed to various gynecologic conditions, as previously has been indicated. Simple ovarian cysts and fibromyomas usually give no pain until their size is sufficient to produce some sensation of weight. Some alteration of menstrual disturbance may serve to call attention to the pelvis, when examination will reveal the tumor. Endometriosis may give rise to acquired dysmenorrhea, with pain referred from the pelvis toward the sacrum; pelvic examination is necessary for diagnosis. Perineal relaxation, with associated cystocele and rectocele, as a result of childbirth, may also cause lower abdominal discomfort of a bearing-down type.

Genito-urinary Conditions.—Genito-urinary conditions, such as a full bladder or vesical tumor, may give rise to suprapubic aching. Vesical calculi frequently will cause sudden attacks of sharp pain which are aggravated by motion such as walking. Brooks has noted that nausea and vomiting are frequent accompaniments of renal disease. Uremia, particularly when it is the result of chronic prostatic hypertrophy with urinary retention, is especially prone to produce abdominal distress, with vomiting suggestive of peptic ulcer. A careful history and physical examination, together with estimation of the concentration of blood urea and of the amount of retained urine, of course, will establish the diagnosis.

The differential diagnosis of genito-urinary conditions has been considered in greater detail under appendicitis.

Functional Conditions.—Finally, the various functional disorders and neuroses send a large percentage of patients to the physician for diagnosis. Existence of this group of patients would tend to put others in danger if physicians were inclined to sacrifice thoroughness for haste or were inclined to be influenced unduly by the psychic makeup of the patient. Correct diagnosis can be made in this group of cases, however, if every possibility of the existence of organic disease has been adequately investigated. Justification for one of the diagnoses applicable in these cases was given by Macy and Allen in a review of 235 cases encountered at the Clinic. In this group, they found that a diagnosis of chronic nervous exhaustion, made on an average of six and a half years before the final examination of the patient, proved accurate in 94 per cent of the cases. As a large portion of these patients presented evidence of visceral dysfunction, largely in the form of various pain syndromes, it can be seen that the diagnosis was justified. As a rule, the pain of these patients has existed for a comparatively long time without appreciable alteration and without assuming the true characteristics of known organic syndromes. It has a tendency to be vague or bizarre and often extends in unaccountable fashion. It further tends to association with fatigue or with periods of emotional stress and as a rule gives most trouble when the patient has moments of leisure. It is important that in spite of all this discomfort the general condition of the patient is usually unchanged from his normal one and the various examinations give uniformly negative results.

THE ESSENTIAL KNOWLEDGE AND VIEWPOINT

In conclusion, an essential to the correct diagnosis of abdominal pain is knowledge of familiar pain syndromes and of the various lesions which may simulate these. It is necessary to possess a high threshold of suspicion for disorders which may exist and to investigate these thoroughly when ordinary methods fail to substantiate first impressions.

FUNCTIONAL DISTURBANCES OF DIGESTION

WALTER C. ALVAREZ

THE most important thing to do before treating any patient with gastro-intestinal disease is to make as exact a diagnosis as possible. In a large percentage of cases if the physician will only take time at the beginning to secure an adequate history, the cause of the trouble will become fairly obvious. The digestive tract is so exceedingly sensitive to nervousness, worry, anger, and fatigue that, of all physicians, the gastro-enterologist must be the one most concerned to learn something of the patient's temperament, of his sorrows, and his problems of life in home and office and shop. Actually, even when an organic disease is found, such as an ulcer in the duodenum, it still may be essential that the physician delve into the patient's private life to learn of such things as financial reverses, marital unhappiness or bad nervous habits, which commonly give rise to a peptic ulcer and later help to keep it active.

I would emphasize that as a rule the physician should make the diagnosis of a functional digestive trouble not by exclusion; not simply because he cannot find any organic disease, but because the symptoms complained of are typically those of a well-known functional disturbance, or because an obviously fussy, worrisome, fidgety, weepy, constitutionally inadequate, or half crazy patient tells his story and behaves during the examination in a typically neurotic way. We physicians all dread meeting the woman with such a multiplicity of complaints that she comes to the first interview with a written list of them: we know immediately that she probably hasn't much seriously wrong with her, and we know that our therapeutic results will not be brilliant.

The great advantage of making the diagnosis of a neurosis at the start, positively, is that if, during the various physical

and laboratory examinations which must always be made before the patient can safely be reassured, something be found such as an apparently silent gallstone or duodenal ulcer, or a few amebas in a constipated stool, the physician will not immediately jump to the conclusion that all the patient's troubles are due to cholelithiasis, duodenal ulcer, or amebiasis. Actually, as years of practice bring a man wisdom, he becomes less and less inclined even to mention these abnormalities to the nervously harassed patient, and he becomes more inclined to insist on the essential fact that the main trouble is a neurosis which cannot be cured by any amount of tinkering at some one or two organs of the body. Anyone who takes thought ought to be able to see how unlikely it is that the removal of a dead tooth, or tonsillar tags, or a hemorrhoid, or even a gallstone could change a frail little complaining, jittery, psychopathic girl into a normal healthy woman; and yet the performance of this miracle is being attempted many times a day in nearly every hospital of the land.

Many physicians feel that they cannot afford to take the time to listen to a long history. They are too busy, and there are too many patients waiting outside in the anteroom; but actually if a physician does not take adequate and informative histories, and if he regularly looks to the roentgenologist and the laboratory girl for the diagnosis, he is bound to make serious mistakes, and during the course of weeks or months he is sure to waste many hours of time on misdirected and therefore futile treatments.

For instance, if an old man's belching and heartburn and high epigastric distress after a big dinner are due purely to a narrowing of a coronary artery, and the physician does not get the history of attacks of anginal pain on effort or after the loss of temper, what can he hope to gain by trying various diets, carminatives, and colonic vaccines? I could easily present here scores of case reports which would show how true it is that the physician can, in the course of a busy year, save himself many hours of effort if he will only listen to the patient's story for a longer time at the beginning.

Here, for instance, comes a recently married woman with giant urticaria. She has been skin-tested several times, and hours have been spent on leukopenic indexes and on trying

to adjust elimination diets. She has been given injections of calcium, epinephrine and peptone, and her digestive tract has been studied roentgenologically time and again. Finally, when someone takes the trouble to sit down and chat with her long enough to get acquainted, he learns that the urticaria came within a few hours after she was shocked by the discovery that her husband has a child by his old mistress whom he is still supporting. He learns also that when this patient went home to mother for a while and calmed down a bit, she became almost well, in spite of the fact that she went back onto a full diet.

Obviously, it is highly important that the gastro-enterologist see his patients as human beings in their setting at home and in the office. He must know something also of their ancestry, and much will become clear to him when he finds that a queer, inadequate, uncommunicative and unfriendly patient has several insane relatives. I feel sure that this type of heredity commonly accounts for a group of symptoms which suggest that the autonomic nervous system is extremely unstable and given to playing miserable tricks on the patient. In many cases it accounts also for nervous breakdowns, mild depressions, and extreme feelings of fatigue or toxicity which are otherwise unexplainable. Often it accounts for the inability of a healthy looking man to work or to earn even a meager living. Such a man rarely seems to realize that his digestive troubles are due to the fact that he is psychopathic and poorly adjusted to life among his fellows. Usually he blames all of his disability on some vague indigestion or pain in stomach or colon, and he may feel so sure that poisons elaborated in the bowel are destroying the brain that he will almost beg surgeons to operate on him, not once, but several times.

In many cases the physician should know that the patient before him is caught in a miserable situation at home from which there is no possible mode of escape. How can he hope to help a woman with diets or sedatives or operations when she is fighting day and night with a man whom she hates and despises but whom she cannot well leave because if she did, she and her children would be penniless? Or how is one to help the headaches, backaches, and stomach aches of a shop girl who, because of dire need must stick to the uncongenial

job which is draining all of her strength? How can one cheer her up when the need for supporting aged parents is making marriage and escape impossible for her? Or how can one hope to cure the young lawyer who has failed in his bar examinations and whose only prop to self-respect is now his illness?

Often I have to say to patients after I have heard the history of misery or overwork, that the only way in which I could possibly cure them would be to get from some benevolent insurance company an annuity which would assure them of, let us say, \$150 a month for life. And usually they admit that this would do the trick because it would free them from daily contact with a hated person or job and it would free them from those terrible fears of the future that keep them awake at night.

Unfortunately, because these people keep hoping against hope that they will some day be cured by some prescription or diet or operation, they generally keep going the rounds, and sooner or later they part cheerfully with teeth or tonsillar tags or some detachable abdominal organ.

So far I have talked of the great advantages that accrue to the patient when a careful history is taken at the start. Actually there are advantages also for the physician. By first getting a good understanding of the psychic problems, he can save himself or the institution in which he works from wasting much money on laboratory reports which contribute nothing to the diagnosis. The young physician who rushes ahead and orders a hundred dollars' worth of laboratory and roentgenologic work, commonly finds himself later holding the bill because the constitutionally inadequate and psychopathic patient is often compelled to live off of relatives who are almost as badly handicapped and as poor as he is. I am not arguing that the poor be examined superficially just because they cannot pay; when a shop girl comes with a fever for which no cause can be found, of course every nook and corner of her body must be searched for infection, no matter what it costs the institution caring for her; but when one finds that a poor old farmer with an inoperable carcinoma of the stomach was sent by a methodical young assistant to several specialists for a thorough check of focal infections, one cannot help being annoyed, first, because the tired old man had to be needlessly bothered, second, because a supposedly educated man should

be so thoughtless, and third, because the expense would have to be borne by the clinic. Even if the man had been a millionaire, it would have been a crime to pass these bills on to him.

Naturally in most cases, even when the physician is certain from the history that the troubles are functional in nature, he must make some examinations before he has a right to assure the patient that nothing serious is wrong. As everyone knows, it is perfectly possible for a tired, overworked, and psychopathic girl to have tuberculosis or a tumor of the uterus; and besides, a careful examination is one of the best vehicles for psychotherapy. The point I want to make is that after a patient with an obvious neurosis has once been examined thoroughly in a fine medical institution or by one or more able physicians, all of this work need not promptly be repeated, as it so commonly is nowadays, by the next physician who is consulted.

Unfortunately, this next physician often feels compelled to order a number of tests which he knows are not likely to reveal anything important simply that he may protect his reputation in case the patient, in further shopping around, should fall into the hands of that type of young doctor who prides himself on the machine-like way in which he orders every conceivable test done on every patient who comes to see him.

To show what I mean: Recently, while examining a hopelessly neurotic and constitutionally inadequate girl, I was particularly careful not to run up a bill for laboratory tests because I felt so sorry for the fine young mechanic, her husband, who obviously was doomed to a life of servitude to physicians and hospitals and drug stores. Imagine my disgust, then, when a few weeks later I received a nasty letter from the wife saying that she had at last found a *good* doctor who had put her through a score of tests and had found that she was in a bad way with a low basal metabolic rate of -14 , a beginning diabetes with a blood sugar of 120 mg., a dangerously low blood pressure of 100 mm., a badly dropped colon, and a terribly diseased appendix which held the barium for twenty-four hours! She wanted to know how it was that the clinic could keep on its staff a man as careless and as ignorant as I.

Now, I would gladly admit my ineptness as a physician in this particular case if I thought that the man who had so

pleased this woman by catering to her hypochondriasis had really brought her nearer to health or had so won her confidence that he could eventually talk her out of her troubles, but I much fear that by now she is decidedly the worse for having been firmly saddled with several new neuroses and phobias. Actually all medical irregulars and quacks know the value of impressing the patient with an extensive examination with much electric apparatus, and many is the time I have had a patient tell me that although her back manipulator may not have cured her, she still admired him because she got from him a far more thorough examination than she ever got from any regular physician, including myself. My answer to such a woman is that I could easily send her for thirty different types of examination, but I would rather use my judgment in choosing those that are likely to contribute something to the diagnosis. If I were to make a practice of ordering all tests for every woman who came into the office, I would be either a fool, a senseless machine or a robber.

Actually, it would be much better for some patients if they knew that the wiser the physician the fewer tests he needs. To show what I mean: By asking a few questions, feeling the patient's skin for warmth and moisture, counting the pulse, watching the mobility of the face and the way in which the patient either fidgets or sits still, and by checking a few reflexes, the experienced clinician will often satisfy himself that the basal metabolic rate must be within normal limits and that it need not be measured exactly; or after glancing at the pulsations in the neck and asking a few questions he will feel safe in dispensing with an electrocardiogram. In his later years Sir James Mackenzie used to get actually angry when at a consultation on a heart case the attending physician would talk much about electrocardiograms and polygraphic tracings. The greatest heart specialist in the world had come to see that he could tell most about a man's heart by asking him questions. What he wanted to know was: how far could the man walk without getting pain and dyspnea; that was the best index he had found to function and the best guide to prognosis.

Another big point I would emphasize is that although the physician does well when he recognizes clearly that the troubles of a patient are functional, this is not enough; he must go

further with his study until he knows what type of functional trouble is present and what is the cause. There is no use in saying to every patient with a functional indigestion that nothing is wrong; that he must forget it, and must take some bromides and belladonna and go on a smooth, high-vitamin, anti-constipation diet. This prescription, which I fear is almost routinely handed out in some offices, must often fail to help because although it may be of some value to a person who has an anxiety neurosis with constipation and some jitteriness, it won't help those hundreds of sufferers who have other types of functional indigestion.

Only a little encouragement and reassurance is needed by the sensible patient who says, "Well, if there is nothing serious growing in my abdomen or my head, I can easily stand this gas or pain or distress or headache; I will go back to work and will stop worrying." But bromides and a high-vitamin diet won't help a bit if the patient's indigestion happens to be due to a tremendous sensitiveness to milk or eggs, and it will not help if the abdominal distress and cecal soreness are due to constipation which cannot be controlled for any length of time by the use of a bulky diet. Bromides and a diet will not help the overworked girl with a sensitive colon who is terribly unhappy because her beau cannot marry her and at the same time support his aged parents. Nor will they help the woman who is fighting with her husband and trying to make up her mind about a divorce. They won't help the patient whose abdominal distress is a variant of migraine, and they won't help the old man or woman whose misery is due to an unrecognized stroke, or a failing heart, or a depressed state with suicidal tendencies. They will not help the unrecognized insanity of the woman who thinks that her abdominal distresses (probably hallucinations) are due to an intestinal obstruction which is producing toxins that are destroying her brain, and they will not help in those common cases in which a woman's disability seems to be due primarily to some failure in the functions of the several glands which produce normal femininity and a normal menstrual cycle.

"Mucous Colitis."—One of the commonest types of functional disturbance is that in which the large bowel is hypersensitive and sore to the touch. The more I see of persons

with this type of trouble, the more I want to leave the bowel alone and to treat the mental and nervous troubles of the patient. One cannot hope to get anywhere with these patients until one can convince them that they haven't a true colitis with an inflamed and ulcerated mucosa. They must be freed from the fear that they have an organic disease which can some day bring them to death's door.

I always assure them that in thirty years of practice I have never seen the so-called mucous colitis kill anyone, and I try to make them see that what they have is only a hypersensitive-ness, often inherited, which is not curable in the ordinary sense of the word because it will probably reappear at intervals throughout life. I stress the point that the proctologist saw a normal mucous membrane when he looked into the bowel, and I explain that when some roentgenologists diagnose "colitis" they do not mean that they saw an inflamed or ulcerated bowel; they are just unfortunate in using a term which many physicians now feel strongly should be reserved for organic disease of the colon. It only makes for confusion and trouble to use it in describing a hypersensitive and spastic colon.

One can help these patients best when one can reassure them and can get them to do some detective work to discover and identify the several influences that in them can bring on an attack of soreness. Often it is emotional strain or excitement or the neglect of constipation, or the eating of certain foods to which the individual is sensitive, or the coming of a cold, or the taking of a laxative.

Sometimes all one needs to do with these people is to get them to see that their troubles are due largely to their unhappiness and the constant strain of a frustrated life. Often again one can give them great relief by teaching them to relieve constipation by a daily enema of physiologic saline solution, and in other cases one can work what is almost a cure by removing one or more irritating foods from their diet.

Some women who have become recluses because the sensitive bowel fills with gas and mucus, and torments them whenever they go out, especially with an attentive man, can be set free by the prescription to take a little codeine or paregoric just before they leave the house.

The Patient Who Is Food-sensitive.—In a certain per-

centage of cases of indigestion some at least of the symptoms for which the patient seeks relief are due to the eating of certain foods to which the person is highly sensitive. Often the patient knows of a few such idiosyncrasies, but he doesn't know that he is sensitive to some food such as eggs which he eats almost every day, or if he knows that he is sensitive to eggs, he hasn't thought to stop eating cakes and puddings. Commonly the discovery of the trouble-makers requires much detective work in which the patient must join with the physician.

There are two main ways of finding out which are the offending foods, and the physician's choice of these ways must depend on how the symptoms appear. When the indigestion or pain or gas or migraine comes in attacks at intervals of weeks or months, the cause can best be found by making each time a written record of the unusual foods—those not eaten every day—consumed in the twenty-four hours preceding the upset. Most suspicion should fall on foods eaten at the meal which preceded the upset. After three or four attacks have been experienced, the record may show clearly that one particular food was eaten before each upset. This food should then be left alone to see if relief is obtained.

When, however, the distress is present almost every day the problem of finding the offending food or foods must be simplified by reducing the number of possibilities. Usually I ask the patient to eat, for two days, nothing but lamb, rice, butter, sugar, and canned pears. If on this diet he loses all his distress, I begin to give him one new food each day added to the others until I find those which cause upsets.

Occasionally the skin-sensitiveness tests will help to throw light on the problem, but usually they do not, and sometimes they are a nuisance because the patient is prone to believe that the implications derived from the skin tests are right, and that he must never again touch the foods which produced wheals. Actually no conclusions can be drawn until the suspected foods have been tested several times by actual ingestion. As is now well known, the skin tests are of value principally in the discovery of the pollens and dusts which cause hay fever and asthma. Apparently there is a closer connection between the sensitivenesses of the skin and the mucous membranes of the

nose and lung than between the sensitivenesses of the skin and the digestive tract.

Constipation.—A common form of indigestion is that due to constipation. The presence of a fecal plug in the rectum seems often to lead to the formation of gas; it causes some reverse peristalsis or back pressure in the tract, and fecal material stagnating in the cecum eventually irritates the mucosa there; at times it causes shallow ulcers and often it produces pain which is mistaken for that of chronic appendicitis. Distention of the rectal wall can also disturb the brain, producing symptoms such as dull headaches, which are commonly assumed to be due to the absorption of toxins but which I think are more often due to pressure on nerve endings, because they usually disappear immediately after defecation.

In many of these cases all the physician has to do to cure the patient is to find some means of removing the fecal plug from the rectum or left side of the colon without at the same time upsetting the stomach and the whole small bowel. Commonly the patient has been unable to do this comfortably either with purgatives or a bulky diet. The purgatives make more gas and indigestion, and the bulky diets, if they work at all, work well for only a few days or weeks. Sometimes in such cases the secret of success is to shift every ten days or so from one of the now popular gummy bulk-producers to another.

In other cases the ideal treatment is a daily enema of physiologic salt solutions. Many physicians fear enemas, but in twenty years of searching I haven't yet been able to find a man or woman with a colon which seemed to have been injured by years of enema-taking. Patients should take the enema while seated on the toilet seat and should expel the water as soon as it is run in.

The Constitutionally Inadequate Person.—A large percentage of the gastro-enterologist's practice is made up of those persons who were born with a frail type of body into which "poor materials" seem to have entered. I am inclined to think that the most defective and troublesome of all the organs in the bodies of these people is the nervous system. It is because of this defect that they cannot stand the ordinary strains of life. Any little break in routine, any conflict with other human

beings, any hurry, or any prolonged effort leaves them worn out. I know a charming woman of culture and wealth who gets all worn out and comes down with a severe migrainous headache whenever she begins to think of the effort which she will have to make in letting her maid dress her and her chauffeur drive her from her New York home up to her summer place in Connecticut!

Relatives of the Insane.—In many cases I find on careful questioning that the constitutionally inadequate person with sensations of extreme fatigue is a *relative of the insane*. As I have already pointed out, relatives of the insane often suffer from symptoms which are best explained by assuming that the autonomic part of the nervous system is unstable, and that the poor victim is constantly being upset and tortured by unnecessary outpourings into the tissues of powerful substances such as acetylcholine, sympathin, epinephrine, and histamine, which we now know are formed as a result of activity in nerves or in smooth muscle. It is no wonder that these patients are so uneasy and frightened when the body is behaving so erratically; when the heart is intermittently stopping or racing, or when because of feelings of faintness, sinking, dizziness or nausea, or because of flushings, sweatings, waves of gooseflesh in the skin or feelings of numbness or approaching paralysis, it seems as if death must be near.

The Psychopathic and the Mildly Insane.—Because most of us physicians never had any training in psychiatry it is no wonder that we commonly fail to recognize the earlier and milder stages of insanity in our patients, and fail to see that many of those who consult us about their stomach should really be in the office of a psychiatrist complaining about mental depression, phobias, fears of suicide, and an inability to live comfortably and easily with their fellows. After all my efforts to recognize these patients I am astonished now and then to learn from relatives that a man or woman, who, during several interviews in the office, was pleasant and sensible enough, is definitely crazy and a terrible problem at home.

If one who is always watching out for patients with the milder types of insanity fails to recognize them, how much more often must those physicians fail who take only a cursory history and see their patients for only a few minutes at a time?

To show what I mean: One day I saw an insurance salesman who came to the Clinic ostensibly for the repair of a hernia. I became suspicious of him because he seemed too talkative and affable. I then learned from friends that the man's family had brought him to the clinic with the hope that some physical cause would be found to explain the recurrent spells of depression which had put a stop to his earning power. During these spells he would do nothing but sit in a darkened room all day wringing his hands and weeping over his unworthiness.

Curiously, neither the man nor his family mentioned these spells or the insanity in the forebears, but I suspected from his exaggerated gaiety and talkativeness that he must be on the top of a short manic-depressive wave. Similarly, I was led to the discovery of a manic-depressive cycle in an attractive young woman when I noted that during her stay in the hospital following a major operation she was never in her room but always all over the place making friends with everyone. When questioned she confessed that she happened then to be in an exalted stage and that later she would be depressed, worn out, and disposed to blame all her troubles on an irritable colon.

Spondylitis.—Another disease which commonly sends patients to the gastro-enterologist with complaints of abdominal pain is a chronic smoldering infection about the spine which affects the nerves emerging from it. There is many a patient who would have been spared an abdominal exploration if his physicians had only been taught to think of this very common disease as a cause of abdominal pain. I always think of it when I find that the pain has no definite relation to any function or any organ in the abdomen. It does not come at any time in the digestive cycle, and it is neither better nor worse for eating or for emptying the bowel. The thing that does influence it is usually movement of the body. Commonly it comes when the victim sits or lies in one position for a while, and it improves when he or she gets up and moves about. It also is likely to be worse after some infection such as a cold.

In many cases one can get a most helpful history of attacks of lumbago, sciatica, stiff or painful neck, "cricks" in the back, sacro-iliac strain, or generalized arthritis. Sometimes one can demonstrate a zone of hyperesthesia in the skin, or one can

show by pinching that the soreness is superficial in the skin and subcutaneous fat. It is not deep in the abdomen, and often when this is pointed out, the patient says, "If you had asked me I could have told you that."

Roentgenograms will sometimes show arthritic changes about the points of emergence of the affected nerves, but this evidence of disease is not necessary to the diagnosis because the most important changes are in the soft tissues. Once a sensible patient is assured of the nature of the pain he will often depart saying "That is all I wanted to know; if the pain isn't due to a tumor growing in my abdomen, I can easily put up with it."

Other Types.—There are many other seldom described types of functional digestive disturbance which I now can recognize as entities and old acquaintances, but space does not permit their description here. I might just mention the nervous type of regurgitation which begins immediately after meals. It is not "vomiting" because it is effortless and not associated with retching. Many of the women with this trouble get operated on several times, but I have never seen them helped by any type of operation.

I would like also to emphasize here what appears to be a fact, namely, that migraine is a disease all by itself, and one which is rarely helped by any amount of operating in nose, throat, mouth or abdomen. In most cases I believe the primary storm is in the brain or the meningeal blood vessels, and the abdominal disturbance is secondary.

In conclusion I would emphasize again that in all this work with functional types of indigestion, when it comes to diagnosis and treatment, the physician must depend primarily on a carefully taken history, well considered and skilfully interpreted.

THE ROENTGENOLOGIC INVESTIGATION OF THE SMALL INTESTINE

HARRY M. WEBER AND B. R. KIRKLIN

UNTIL relatively recent times the small intestine had not received the interest and diligent roentgenologic investigation which had been given to the esophagus and stomach above it, and to the colon and rectum below it. Lately we have been



Fig. 84.—*a*, The first step in the examination is a preliminary roentgenoscopic and roentgenographic survey of the abdominal field. Abnormal collections of gas both within and without the intestines are detected and studied; *b*, in the adult, large accumulations of gas in the small intestine are not present normally; in children, gas-filled loops of small intestine are not considered abnormal unless the loops are markedly distended; *c*, small and moderately large collections of gas in the colon are usually not considered to be of significance. This holds true for small amounts of gas in the small intestine as well.

encouraged to believe that a more diligent and persevering application of the roentgenologic method may ultimately bring to the diagnosis of abnormal small intestinal states a degree of accuracy and reliability, favorably comparable to that which it brought to the diagnosis of abnormal conditions of the esophagus, of the stomach and duodenum, and of the colon.

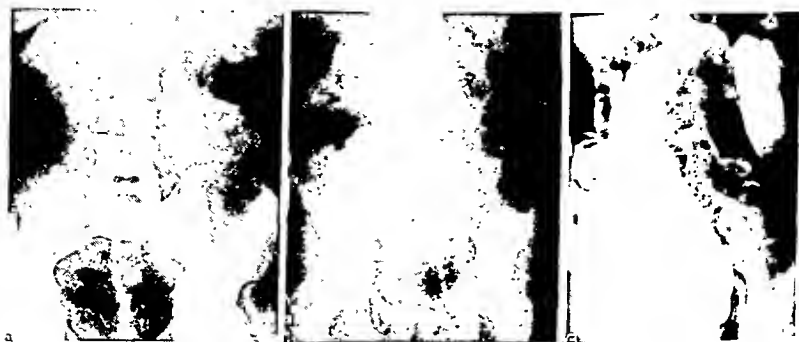


Fig. 85.—*a*, Distention of intestinal loops with gas, or with gas and fluid, is of great significance. The patient represented by this roentgenogram had small intestinal obstruction of low grade, owing to inflammation in a Meckel's diverticulum; *b*, marked distention of small intestinal coils with gas. Examination of small intestine with opaque material administered orally is contraindicated. The examination of the colon (opaque enema) revealed that the patient had an intussuscepting carcinoma of the cecum; *c*, a situation carefully to be avoided. Carcinoma of the descending colon. Marked distention of large and small intestine above the constricting lesion. The opaque material had been administered four weeks before admission. It should not have been administered orally at all.



Fig. 86.—A dangerous degree of intestinal obstruction having been excluded, the opaque material is administered orally. *a*, A simple suspension of barium sulfate in water is the most satisfactory of all preparations; *b* and *c*, at the first roentgenoscopic session the examiner tries to express as much as possible of the suspension from the stomach into the small intestine. The duodenum and the upper coils of jejunum can be examined within the first few minutes. Roentgenograms, with or without general or localized compression, are made at the examiner's discretion.



Fig. 87.—The small intestine will accept only a certain volume of gastric content within a given time, and efforts to make it accept more than this volume are fruitless. *a*, The stomach seems to empty its contents into the small intestine best when its possessor lies on the right side in as relaxed a state of mind and body as possible; *b* and *c*, roentgenoscopic and roentgenographic examinations are made at as many intervals as the examiner finds necessary to permit him to visualize and manipulate each small segment of the intestine.



Fig. 88—*a*, As soon as the stomach has given up all but a small amount of the opaque suspension, the patient is invited to partake of a palatable breakfast. This is done to stimulate the normal peristaltic activity of the intestine and to diminish separation of the opaque meal into numerous small collections distributed widely along the intestinal tract. Distention of the loops of small intestine with opaque material is the aim throughout the examination; *b*, immediately after breakfast, *c*, fifteen minutes after breakfast.



Fig. 89.—In the lowermost segments of the small intestine these conditions prevail: (1) the coils are clumped together low in the abdomen, and are relatively inaccessible to manipulation; (2) the motility has been considerably retarded; (3) dehydration of the opaque suspension has already begun to take place. These segments are therefore examined in a more satisfactory manner by filling them with the opaque suspension by enema. After the opaque material has been evacuated from the colon the ileal coils are elevated out of the pelvis and are readily examined. *a*, Patient ready to take the opaque enema; *b*, colon and terminal ileum distended with opaque enema; *c*, colon and terminal ileum after evacuation of opaque enema.



Fig. 90.—A series of roentgenograms showing the first stages in the examination of the small intestine. *a* and *b*, The progress of the meal before the period of relaxation; *c*, the progress of the meal after the patient has been lying on the right side for a short time. It is to be emphasized that the roentgenoscopic examination is of greatest value, and that no number of roentgenograms can replace it.

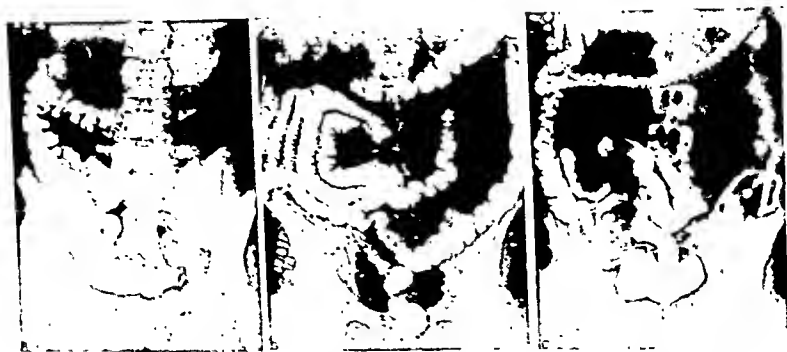


Fig. 91.—The examination of the small intestine continued. *a*, The progress of the meal after breakfast has been taken; *b* and *c*, the lowermost coils of ileum are visualized by filling them with the opaque suspension in retrograde direction through the ileocecal orifice.



Fig. 92—Diverticula of the duodenum are not uncommon. Only rarely do they have clinical significance. *a*, A large diverticulum in the second portion of the duodenum; *b*, multiple duodenal and jejunal diverticula. Single and multiple diverticula occur in the jejunum and ileum but more rarely than in the duodenum. They may be large or small, and rarely assume clinical significance. *c*, solitary diverticulum in the ileum thought to be a Meckel's diverticulum. The patient had no symptoms referable to this finding.

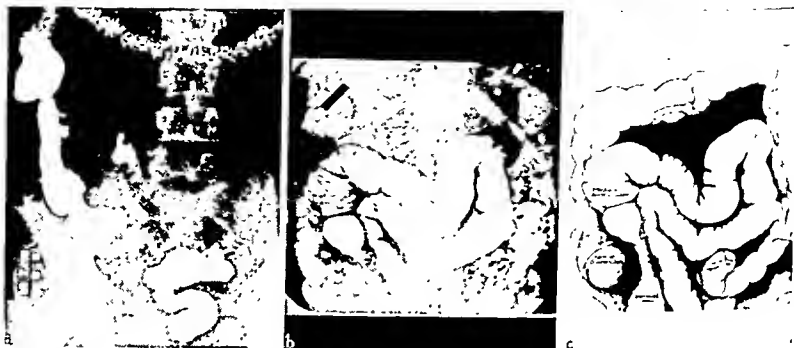


Fig. 93.—*a*, Meckel's diverticulum found in association with hyperplastic ileitis. The finding was verified at surgical exploration; *b*, a large Meckel's diverticulum. The patient was a man, thirty-five years of age, who had symptoms of intermittent intestinal obstruction for one month; *c*, interpretation of the foregoing roentgenogram. The preoperative roentgenologic diagnosis was carcinoma of the ileum. A review of the roentgenogram after operation made the interpretation possible.

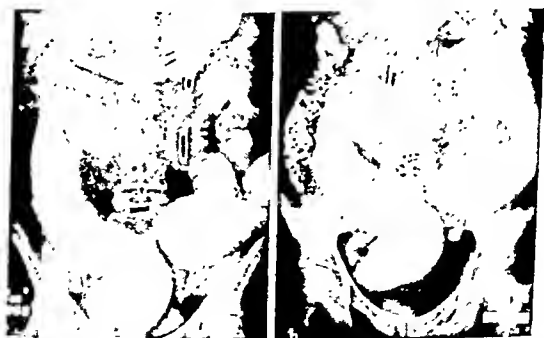


Fig. 94.—*a* and *b*, Carcinoma of the lower jejunum. The patient was a woman, sixty-seven years of age, who had symptoms of intestinal obstruction, increasing gradually in severity, for one year. The lesion was resected. It was a low-grade annular adenocarcinoma without involvement of lymph nodes.

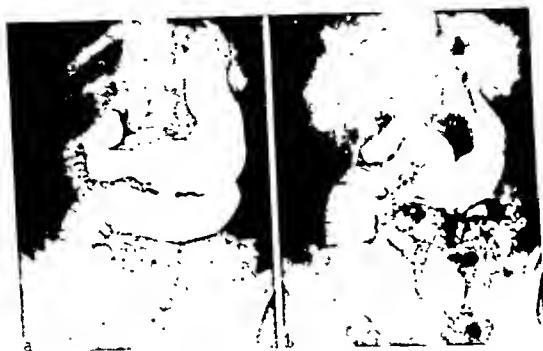


Fig. 95.—*a* and *b*, Carcinoma high in the jejunum. The patient was a woman, fifty-seven years of age, who had been suffering with upper abdominal pain and vomiting for three months. The actual filling defect is not seen on these roentgenograms but a roentgenoscopic diagnosis of carcinoma of the jejunum was made. A very malignant annular carcinoma of the jejunum was resected. There was marked involvement of lymph nodes.

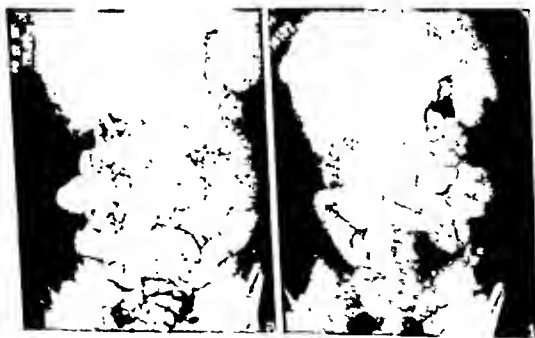


Fig. 96.—*a* and *b*, Carcinoma low in the jejunum. The patient was a man, forty-three years of age, who had had vague abdominal symptoms for more than three years. His chief symptoms were weakness, loss of weight and pallor. The roentgenologic diagnosis of carcinoma of the jejunum was verified at operation, but the patient had metastatic lesions in the mesenteric lymph nodes and liver.

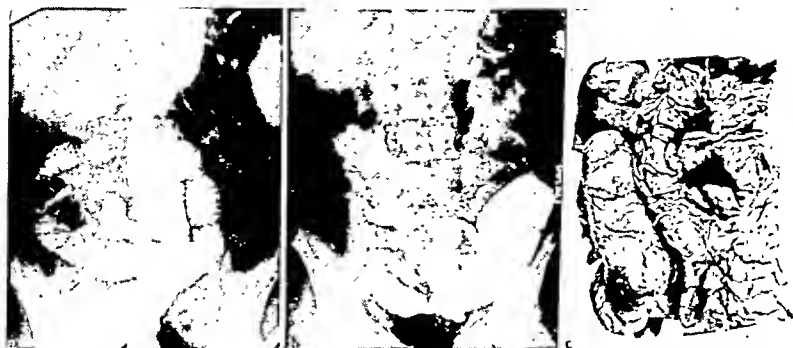


Fig. 97.—*a* and *b*, Sarcoma of the jejunum. The patient was a man, forty-four years of age, who had had indefinite abdominal symptoms for one year, and a mass in the right abdomen for six months. At operation the lesion was shown to be an inoperable, very malignant, sarcoma. The patient died on the tenth postoperative day; *c*, the specimen was obtained at necropsy.

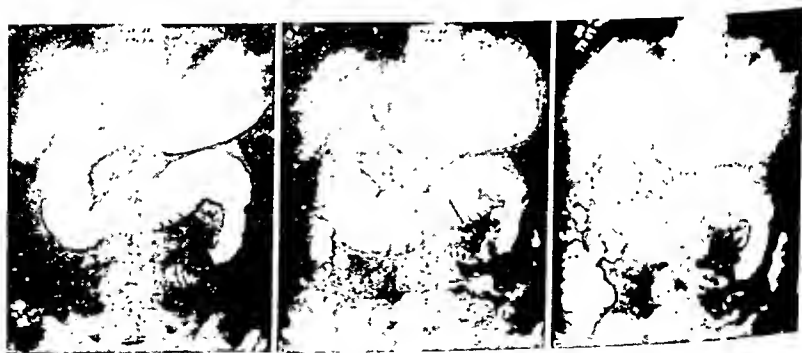


Fig. 98.—A non-neoplastic tumefactive lesion of the jejunum. The patient was a man, thirty-eight years of age, who had symptoms of intestinal obstruction gradually increasing in severity, for eighteen months. The roentgenologic diagnosis of non-neoplastic tumor of the jejunum was confirmed at operation, although the surgeon discovered another similar lesion at a lower level in the small intestine. *a*, June 29, 1935; *b*, July 1, 1935; *c*, July 2, 1935.



Fig. 99.—*a*, *b* and *c*, Tumor of the head of the pancreas ulcerating into the duodenum. The patient was a man, fifty-two years of age, who had several gastro-intestinal hemorrhages, and considerable abdominal distress with vomiting over a period of one year. At the preoperative roentgenologic examination the lesion was thought to be an ulcerating neoplasm primary in the duodenum.

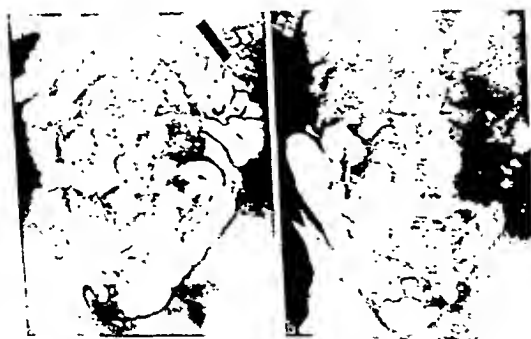


Fig. 100.—*a* and *b*, Sarcoma of the mesentery of the jejunum ulcerating into the lumen of the jejunum. The patient was a man, sixty-five years of age, who had had vague abdominal distress and secondary anemia for several years. The preoperative roentgenologic diagnosis was extrinsic lesion ulcerating into the small intestine. The lesion could not be resected.

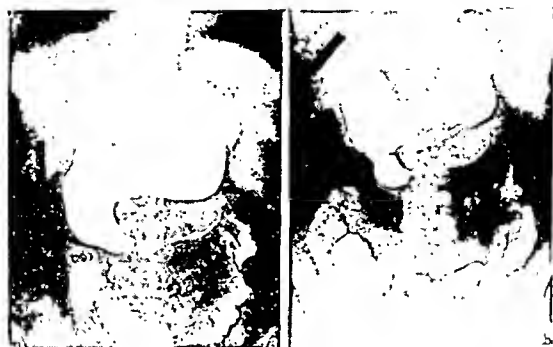


Fig. 101.—*a* and *b*, Extensive involvement of the duodenum thought to be an extension from an inflammatory or neoplastic lesion of the pancreas. The patient was a woman, fifty years of age, who had had abdominal cramps and vomiting immediately after meals for eight months. The patient refused surgical exploration. The diagnosis is therefore unconfirmed.

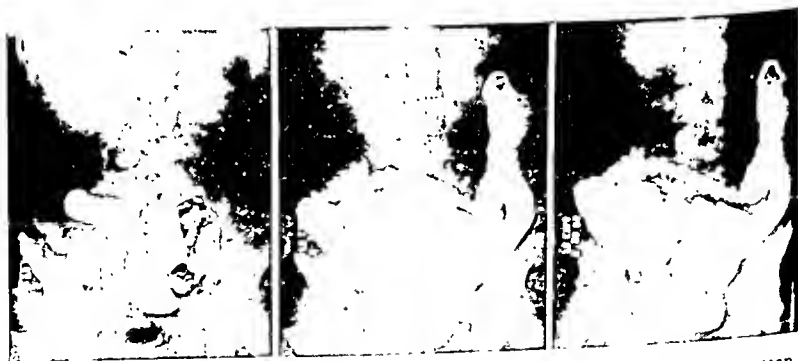


Fig. 102.—Hyperplastic ileocolitis. *a*, The narrowed loop of ileum as seen after an opaque meal; *b* and *c*, the deformed segments of the terminal ileum, cecum and ascending colon as they are seen at the examination using the opaque enema. The diagnosis was confirmed at operation. Evidence of tuberculosis could not be found in the resected specimen. The patient was a man, twenty-two years of age, who had had soreness and abdominal pain for eighteen months.



Fig. 103.—The drawing (a) illustrates the morphologic changes in hyperplastic ileitis; b and c, how these changes look roentgenologically. The length and caliber of the involved segments are reduced, the bowel becomes stiff and rigid, mucosal ulceration may or may not be present. The patient was a woman, twenty-seven years of age, whose chief symptoms, diarrhea, weakness, and abdominal pain, had been present for more than three years. The diagnosis of hyperplastic ileitis was confirmed at operation, although no specimen was removed for microscopic examination. Ileocolostomy was performed.



Fig. 104.—Tuberculous hyperplastic ileocolitis. a, Extensive fibrous and cavernous pulmonary tuberculosis involving the right lung; b, the changes in the ileum and colon shown after the opaque enema had been evacuated; c, the changes after the colon and ileum had been redistended with air. The patient was a physician, thirty-three years of age, who had pulmonary symptoms for eleven years and intestinal symptoms, cramps and diarrhea, for one year. The changes in the intestine seen in this series are contrasted with those in the series which follows.



Fig. 105.—Nontuberculous hyperplastic ileitis. *a*, Normal thorax; *b*, the changes in the ileum and colon after the opaque enema had been evacuated; *c*, the changes after the colon and ileum had been redistended with air. The patient was a man, forty-eight years of age, whose symptoms, diarrhea, weakness, and cramps, had been present for three months. No evidence of tuberculosis could be found in the resected specimen. The smooth, diffuse character of the deformity of the nontuberculous process is contrasted with the rugged, uneven character of the deformity of the tuberculous process in the preceding series.

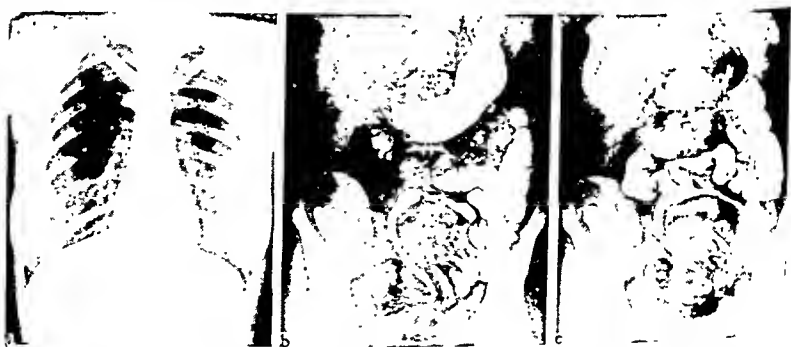


Fig. 106.—Tuberculous hyperplastic ileitis. *a*, Normal thorax; *b* and *c*, the deformity (narrowing, shortening) of the terminal ileum is outlined by the opaque meal. The patient was a woman, twenty-four years of age, whose symptoms, diarrhea, abdominal soreness and weakness, had been present for more than four years. Ileocolostomy was performed. The patient died on the fourth postoperative day. At necropsy the intestinal process was shown to be tuberculous, but no other evidence of tuberculosis was found in the body.



Fig. 107.—Nontuberculous hyperplastic ileitis. *a*, Normal thorax; *b*, the deformity of the ileum as exhibited by the opaque meal, and *c*, by the opaque enema. The patient was a woman, thirty-two years of age, whose symptoms, occasional spells of diarrhea and abdominal soreness, had been present for about two years. The patient died suddenly while anesthesia was being induced preliminary to exploration for hyperplastic ileitis. The roentgenologic diagnosis of hyperplastic ileitis was confirmed at necropsy. No evidence of intestinal tuberculosis was elicited. Again the smooth, even contours of the segments affected with the nontuberculous process are contrasted with those seen in the preceding series.

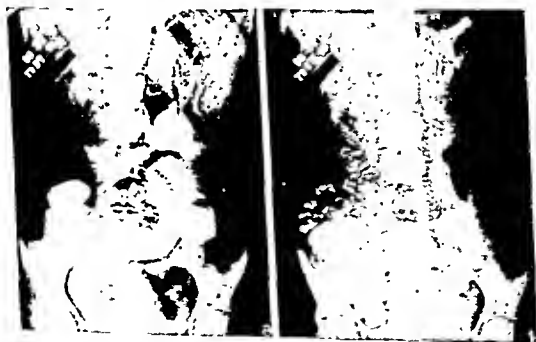


Fig. 108—*a* and *b*, The changes seen in the small intestine in nontropical sprue. A fairly pronounced hypomotility is the rule, and the mucosal pattern of a limited or large part of the small intestine is markedly changed. The roentgenologic changes seem to be owing for the most part to the intestinal atrophy, and to the abnormal intestinal secretions found in this and other deficiency states.

These illustrations were collected and arranged, (1) to describe the conduct of a roentgenologic examination of the small

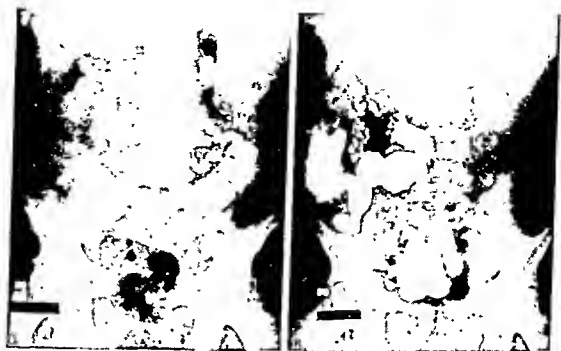


Fig. 109.—*a* and *b*, The changes seen in steatorrhea of pancreatic origin. These are similar in all respects to those seen in other deficiency states and may perhaps be explained on the same basis.

intestine, and (2) to exemplify the roentgenologic manifestations of those abnormal intestinal states which are most fre-

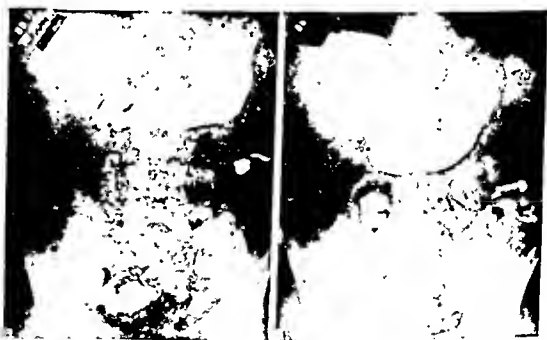


Fig. 110.—*a* and *b*, Pellagra. The changes in the small intestine and colon are similar to those seen in other deficiency states. Marked hypomotility is the rule. The changes in the mucosal pattern may be explained on the basis of the hypomotility and the abnormal intestinal secretions. Atrophy is the only morphologic change which might be held accountable for the roentgenologic findings

quently encountered. Thus it is a fairly complete but brief atlas, and is presented in the hope of stimulating a wider application of this very useful diagnostic procedure.

SOME PRACTICAL PROBLEMS OF DISEASES OF THE COLON

E. G. WAKEFIELD

ALL diseases of the colon, except neoplasms and some granulomas that have not produced too much deformity of the lumen, should be treated medically. However, a disease of the colon that usually can be ideally treated surgically may become solely a medical problem and a disease that usually can be treated medically may become uncontrollable while medical treatment is being employed and surgical therapy may have to be resorted to.

Carcinoma of the colon is an outstanding example of a disease that can be treated ideally by complete surgical extirpation. However, when the patient is first examined it too often is found that the disease has progressed to a point where complete surgical removal is inadvisable and that the only possible treatment is palliative medical care. The responsibility for this misfortune often cannot be directly placed, because of the "nature of the disease." Patients who have an inoperable carcinoma of the colon usually have ignored vague symptoms or have had no symptoms until the onset of a slow perforation with the accompanying fever, or massive rectal hemorrhage, acute obstruction, loss of weight, or weakness has forced them to seek relief. These cases in which the patients should have been cured ideally by surgical treatment fall into three groups: (1) cases in which an inoperable malignant lesion is found at the time of the first examination (the operability of a malignant lesion of the colon cannot always be determined without an exploratory laparotomy); (2) cases in which an exploratory operation discloses an inoperable lesion which necessitates a palliative surgical procedure such as an anastomosis or a colostomy; (3) cases in which extensive metastasis contraindicates

removal of a lesion that otherwise would be considered operable. The treatment of inoperable carcinoma of the colon requires the greatest of skill, because the knowledge that a patient is doomed to die does not mean that a genuine effort should not be made to make him as comfortable as possible in the meantime. Variations and changes in the doses of narcotics and sedatives should be made as soon as the dosage becomes ineffective. One should not let the patients know that symptomatic therapy is all that can be employed; occasionally, this opinion will prove erroneous. Special dietary measures for those who have a colonic stoma will be outlined later.

Carcinoma is one of the commonest serious diseases of the colon among patients who are past the age of forty years. The average age incidence of this disease is approximately fifty-five years. It occurs at an age when other serious diseases often occur. The ideal treatment, as has been stated, is surgical. Operation on the colon is a serious major procedure even if performed by a skilled surgeon. Often, two major operations are required. It therefore is obvious that any patient who is to be subjected to an operation on the colon should be studied carefully for the detection of diseases. This study will determine the proper preoperative and postoperative management and will add to the safety of the treatment and the comfort of the patient.

In a case in which a malignant lesion of the colon is operable, an associated medical disease may lessen the chance that the patient will survive the operation. Such a case requires serious consideration before it is decided that operation is contraindicated. Practically, the physician has little or no choice in the matter. Carcinoma of the colon which is not successfully removed surgically is certainly a fatal disease. A physician assumes an unnecessary responsibility if he forbids operation for malignancy of the colon unless he is thoroughly satisfied that his decision has been based on facts. For practical purposes, a physician has fulfilled his duty when he ascertains that the patient does not have an acute infection of the upper part of the respiratory tract, marked renal insufficiency, congestive heart disease, uncontrolled diabetes, a prostatic obstruction, or some unusual, serious or uncommon disease which contraindicates a major operation.

An acute infection of the upper part of the respiratory tract ordinarily runs its course in a week. If, after this time, the cough has ceased, the lungs are clear to auscultation, the nasopharynx is not congested, and there is no hoarseness, operation can be performed safely. In the absence of definite urinary symptoms and if the specific gravity of the morning specimen of urine is 1.025 and if the grade of albuminuria is not greater than 1 (on a basis of 4), further tests of renal function are superfluous. If the specific gravity of the morning specimen of urine is decreased and if albumin and erythrocytes are present, further study is required, even if urinary symptoms are absent. However, it must be kept in mind that a patient who has a moderate degree of renal insufficiency often will survive a surgical operation. Frequently, in a case in which the patient succumbs to a failing renal function during convalescence, the responses to the tests for renal function have been normal prior to operation. The direct treatment of a failure of renal function that occurs before or after operation has been thoroughly described in many standard textbooks on urology. However, in the treatment of failing renal function, I am sure that it is a mistake to administer more than 3,000 c.c. of fluid intravenously in twenty-four hours. A certain number of patients who have postoperative oliguria will be benefited by omitting the administration of sodium chloride and substituting the intravenous administration of a 5 or 10 per cent solution of dextrose. The best test of the functional ability of a patient's heart is to ascertain what he has been able to do in the way of physical exercise. If a patient who is supposed to have heart disease can sleep with his head on only one small pillow, if he has been able to do moderate physical exercise comfortably, and if there is no dependent edema or congestion at the bases of the lungs, the patient should not be denied an operation for carcinoma of the colon. If he has congestive heart failure, treatment by rest in bed and the administration of digitalis should be given. If there is no edema, digitalization usually may be produced by the administration of a total of $1\frac{1}{2}$ grains (0.097 gm.) of digitalis for each 10 pounds (4.5 kg.) of body weight, in divided doses. After digitalization has been produced, the administration of digitalis in doses which are large enough to maintain it should be

continued. Operation should not be performed until the patient is able to walk around, and even then, it should not be performed without careful consideration.

The known diabetic patient may have carcinoma of the colon. Here, however, I wish to discuss only those patients who are found to have sugar in the urine during the examination for carcinoma of the colon. The care of the known diabetic during a surgical operation has been considered in detail in current literature. Ordinarily in the absence of the cardinal symptoms of diabetes, the discovery of sugar in the urine during an examination for carcinoma of the colon does not indicate serious diabetes. Prior to operation the patients should be given the routine so-called nonresidue diet which is used in the preparation of all patients for operation at the Clinic.

If the urine contains a great deal of sugar after a day or two of observation, 10 or 15 units of protamine insulin may be given if the concentration of blood sugar and other diabetic studies indicate that it is needed. In cases in which the value for the blood sugar is increased definitely, it may be wise to allow the patient to submit to operation unless an acidosis is present. If an acidosis is present this must be adequately treated before operation is performed. Hyperglycemia alone is not immediately dangerous but a mixture of surgical shock and insulin shock is a serious postoperative complication. During convalescence every effort should be made to keep the urine of these patients free of sugar, as is done in the routine postoperative treatment of diabetics.

Occasionally, a patient may have an enlarged prostate that is producing urinary obstruction and at the same time may also have a carcinoma of the colon that is producing obstruction of the colon. In such a case the following treatment is required: (1) immediate relief of the urinary obstruction, and (2) routine treatment of the intestinal obstruction. The ideal procedure is to insert an indwelling urethral catheter and to begin to administer fluids to restore fluid losses and reestablish normal fluid intake and urinary excretion as soon as possible. The medical procedure for relief of the colonic obstruction, when there is also an obstruction of the urinary stream, is the same as when the colon alone is obstructed. The procedure may be outlined as follows: (1) the use of a nonresidue diet;

(2) the oral administration of 1 to 4 drachms (4 to 16 c.c.) of a saturated solution of sodium phosphate, three or four times daily until there is free defecation; (3) rectal irrigations of a 1 per cent warm solution of sodium chloride twice daily while the patient is in a knee-chest position, if the patient is able to assume such a position; (4) application of hot abdominal stupes; (5) occasionally, if vomiting is present, the insertion of a nasal tube which ends in the duodenum will keep the stomach empty and produce a great deal of comfort (it must be remembered, however, that duodenal suction will not empty the colon), and (6) depending on the state of dehydration, fluids should be given intravenously until there is a satisfactory output of urine. The best practical test for dehydration is first to note the decrease in the total volume of urine excreted during twenty-four hours, and, secondly, to note specific gravity of the urine. In severe dehydration the total output of urine may be only 100 to 200 c.c. during twenty-four hours. If the renal function is adequate the urine will be very concentrated, and a specific gravity of 1.030 is not uncommon. If, after twenty-four to thirty hours, the abdominal distention is not relieved it may be well to advise surgical decompression. The choice of operative procedure is a decision for the surgeon to make but a cecostomy usually is desirable. Prolonged overdistention of the intestine is a serious condition. Often, the weakened, overdistended intestine cannot regain its muscular tone even if the condition is relieved surgically. I think it is an erroneous idea for the internist to feel that after he has ordered abdominal stupes, rectal irrigations, sodium phosphate and nasal suction his responsibility has ended and all that has to be done is to continue this treatment and wait for the patient to improve, before the surgeon is called. It is well to repeat that postponement of operation may permit such severe overdistention of the intestine that all of its physiologic elasticity may be destroyed.

There are other medical conditions that may be associated with carcinoma of the colon but all of them cannot be considered here. Secondary anemia frequently is associated with carcinoma of the right half of the colon and with the associated polyposis. Valuable time is always lost if the anemia is treated in any way except by blood transfusions and immediate oper-

ation. In our experience at the Clinic, no compromise can be counselled in the treatment of disseminated polyposis and carcinoma of the colon. Treatment is total extirpation in both cases. Blood transfusions may be given preoperatively.

Diarrhea is not an uncommon postoperative complication after a colostomy. It is usually best treated by diet. When the surgeon feels that the patient may receive an adequate diet, the following diet may be used: for breakfast, 2 ounces (60 c.c.) of orange juice, a serving of a bland cereal with cream, two strips of bacon or an egg, buttered toast and coffee, if desired; for dinner and supper, meat, potatoes, bland dessert without fruit, bread or crackers, butter, cream, jelly and tea or coffee. Fluids or foods are not allowed between meals. When the feces attain a normal consistency, the following fruits may be cautiously added: orange, grapefruit, banana, cooked peaches, pears, apricots, white cherries, apple sauce and baked apples without the peel. Finally, raw lettuce, cooked tomato sauce that is free of peel and seeds, asparagus, beets, string beans, carrots, cauliflower, small peas, and squash may be added. Some patients may find it necessary to adhere to the original diet without any addition for a long time. However, the additions ordinarily can be made during the stay in the hospital, and milk and liquids in small quantities also may be tolerated. As soon as possible, raw fruits and vegetables are added.

In an intermediate position between the malignant diseases of the colon which are ideally treated surgically and the purely medical diseases are the inflammatory processes which produce deformities of the intestinal lumen sufficient to require surgical treatment. Prominent in this group of diseases are the granulomas of the ileocecal segments, diverticulitis, usually in the sigmoid segments, strictures produced by chronic ulcerative colitis, and inflammatory or traumatic strictures of the rectum. The medical treatment of these diseases is essentially the same as that described in connection with the malignant lesions, only that the physician is not so anxious to shift the responsibility to the surgeon except in the cases of granuloma of the ileocecal region, which is strictly a surgical disease if the granuloma is not amebic in origin. Before passing from a consideration of some of the medical aspects of surgical diseases of the colon to

a consideration of some of the purely medical diseases of this organ, I should like to mention briefly the importance of the internist and the general practitioner in assuming with the surgeon the proper attitude and responsibility of the necessity of a permanent colonic stoma. A colonic stoma, when needed, is usually a lifesaving measure. The patient often asks for the opinion of the physician in regard to this procedure. A colonic stoma is a handicap; it should never be made, if possible, without a free discussion with the patient and until he has been told that such is to be done or may have to be done at the time of the operation. The internist or general practitioner is frequently in a better position than the surgeon to discuss this procedure with a patient when it has been definitely decided that such a surgical procedure is required. The physician has no choice in the matter if it is necessary to reestablish the continuity of the colon to the exterior by means of a colonic stoma. For the physician to tell the patient that he would not have a colonic stoma if he were in the patient's place may be compared to a physician advising suicide. All that is required of the physician in such a discussion is to adhere to the known facts, to use tact, and to spare the patient the unpleasant details. It is always expedient to make sure that the patient understands that normal digestion will take place and that good health can be maintained after the formation of a colonic stoma.

The treatment of medical diseases of the colon usually is directed mainly toward the relief of the clinical symptoms which most frequently concern the patient in most cases of disease of the colon. These are diarrhea, constipation, and pain. If one attempts to outline the diseases which often produce diarrhea, it is soon apparent that such an outline will not accomplish all that is to be expected. In the first place, in order to outline treatment, a separation has to be made between diarrhea produced by an intrinsic disease of the colon and diarrhea which is the result of extrinsic disease. The following intrinsic diseases of the colon are associated with diarrhœa: (1) acute colitis (or gastro-enterocolitis); (2) bacillary dysentery; (3) amebic dysentery; (4) chronic ulcerative colitis; (5) uncommon diseases, such as: (a) tuberculous enteritis, (b) bilharzial dysentery, (c) syphilis of the intestine, (d) cer-

tain protozoan infections of questionable etiology. Neoplastic diseases of the colon often are characterized by diarrhea.

Extrinsic conditions that may be associated with diarrhea are: (1) general infections, for example, septicemia; (2) glandular disturbances, for example, exophthalmic goiter and Addison's disease; (3) deficiency diseases, for example, sprue and pellagra; (4) secretory defects, for example, secretory dysfunction of the stomach or pancreas; (5) absorptive anomalies, for example, celiac disease; (6) impacted feces or foreign material, for example, barium; (7) irritation from foods or laxatives; (8) functional disorders of the colon, and (9) diseases of small intestine.

Imperfections in such a list are practically unavoidable. To facilitate examination of some of the medical aspects of these diseases, a few of the more common ones will be considered before taking up the symptom, constipation.

The acute infections responsible for the diseases classed as acute enterocolitis and colitis have been classified by Besredka as polymicrobic and monomicrobic. Acute gastro-enterocolitis is thought usually to be polymicrobic in origin, as mixtures of possible etiologic organisms are usually present. Food infection is thought to be a monomicrobic process; it usually is caused by a number of strains of *Salmonella enteritidis*.

There is no specific treatment for these diseases. Fortunately, they are self-limited. The physician usually sees the patient long after gastric lavage or emetics would be useful. However, if it is thought that emptying the stomach is indicated, the patient can be instructed how to tickle his pharynx. Gastric lavage is an impressive procedure but accomplishes little more than does the index finger when inserted into the pharynx. One dose of one to two tablespoonfuls (15 to 30 c.c.) of castor oil is a priori treatment when the patient is seen early. If the diarrhea continues after the bowel has been emptied, 10 minims of tincture of iodine (0.65 c.c.) in a glass of water should be given three or four times daily. If the diarrhea still continues, 5 minims (0.3 c.c.) of tincture of opium should be given in water every six hours. Tincture of kino is a valuable adjunct to the tincture of opium and the two may be prescribed together in the following prescription:

R	Tincture of opium.....	1.3 c.c.
	Tincture of kino.....	8.0 c.c.
	Mucilage of acacia.....	āā q.s. ad 30.0 c.c.
	Cinnamon water.....	
	Sig.—Take one tablespoonful every two hours.	

Application of heat to the abdomen is often a welcome adjunct.

The proverbial diet of "tea and toast" is a good one during the first day or two of the period of recovery from an acute gastro-enterocolitis. During the first stage of the disease the patient often is unable to take more than small amounts of liquids by mouth, but this is all that should be allowed.

The bacillary dysenteries originate in contaminated foods, water and milk. They are propagated by carriers and flies. The offending organisms are the *Shigella* group. The *Shigella dysenteriae*, the *Shigella minutissima* and the Flexner strain of *Shigella paradysenteriae* are the common offenders. Specific agglutinating sera can be produced against these strains. After the first seven days of the disease the patient's blood contains the agglutinins.

The production of specific agglutinins in the serum does not indicate that specific serum or vaccines are of value in treatment. Experience teaches that the efficacy of specific sera and vaccines is doubtful. However the serum may be tried if available, and the use of polyvalent sera produces the best results. One always should be sure that the patient or the patient's family knows two things about the sera: (1) that the reactions are frequent and severe; they usually last from seven to ten days, and often are accompanied by involvement of the joints; (2) the injections are very painful, and should be given intramuscularly in doses of 10 to 20 c.c. Sera should never be given until the patient is tested for sensitivity to horse serum. After the fourth day of the disease, no improvement is to be expected from administration of the serum. Vaccines may be tried in the cases of chronic disease. Oral administration of physiologic saline solution often is beneficial.

During treatment the patient must be in bed and kept warm; 700 to 1,000 c.c. of physiologic saline solution should be given by mouth early in the disease. Dehydration should be controlled by the intravenous administration of sterile saline solution. Large amounts (250 to 300 gm.) of kaolin may be

administered in twenty-four hours. Hypodermic injections of $\frac{1}{3}$ grain (0.02 gm.) of pantopon may be given one to three times daily.

The diet should be practically nil for the first two days. Then warm teas, lemonade, small quantities of red wine, and 5 to 10 per cent solutions of cane sugar should be given. Solutions of lactose usually are not tolerated. As soon as improvement permits, which is indicated by diminished tenesmus, soups of sago, rice or chicken, or bouillon may be allowed. Gradually, oatmeal and other light cereals, fresh butter, cream cheese and soft boiled eggs are added.

Amebic dysentery is either an acute or chronic colitis that is caused only by *Endamoeba histolytica*. The causative agent is conveyed by food, water, and carriers. There is a tendency for the formation of abscesses of the liver, which may be the first manifestation of the disease.

The therapeutic test that consists of the administration of emetin in doubtful cases is to be discouraged generally. Treatment should not be instituted until a competent parasitologist has found the *Endamoeba histolytica* in the feces. On the institution of treatment, rest in bed hastens the recovery. The application of heat to the abdomen may produce considerable relief if abdominal pain is present.

Emetine and the arsenicals are the drugs of choice in the treatment of amebic dysentery. At the Clinic, if the disease is mild, $\frac{2}{3}$ grain (0.043 gm.) of emetine hydrochloride is injected into the deep subcutaneous tissues twice daily for three days, that is, until a total of 4 grains (0.24 gm.) has been administered. In cases in which the disease is severe we administer individual doses of 1 grain (0.065 gm.) and a total of 6 grains (0.04 gm.) is administered in three days. A week or ten days are allowed to elapse between courses of treatment. Treparsol also is administered during or between the courses of emetine. The treparsol is prescribed in tablets which contain 4 grains (0.24 gm.) of the drug. One tablet is administered three times a day until twelve tablets have been taken. The patient is instructed to chew the tablet and swallow it with food at mealtime. It is impossible to define the total amount of treparsol or emetine that should be administered in an individual case as the therapeutic regimen frequently has to be

altered. The treatment should be governed by the nature of the symptoms and the presence or absence of *Endamoeba histolytica* in the feces. Patients vary in their susceptibility to emetine. Single large doses should never be given. We have not seen any serious reactions from the administration of emetine used as outlined here. The serious reactions which occur from the administration of emetine are circulatory in origin.

In a high percentage of cases of acute amebiasis one course of emetine and arsenic will effect a cure if treatment is instituted early in the disease. In many cases only symptomatic relief will be obtained. Other drugs may be used as adjuncts to emetine.

Chronic ulcerative colitis is a disease characterized by a stubborn chronicity, recurring attacks of abdominal cramps, frequent rectal discharges, fever, and tenesmus. Rectal bleeding often is so diffuse that the bowel movements resemble catsup. A severe secondary anemia commonly is present. The colon loses its haustrations and becomes narrowed, thickened and shortened; the proctologic and roentgenologic appearance is rather typical. The diagnosis is based on the proctoscopic and roentgenologic features. The prognosis, so far as a complete cure is concerned, is often unfavorable in the cases in which the disease is severe and has been present for a long time. Remission of symptoms, however, may occur even in the cases in which the disease is extremely severe and chronic. Remission of symptoms does not always follow special treatment.

The treatment of this disease has aroused considerable interest. Attempts to put the colon at rest by making an ileac stoma has its advocates. If an ileac stoma would put the colon at rest and allow it to heal, this would be ideal. Experience teaches that an ileostomy may be a lifesaving procedure in certain selected cases of chronic ulcerative colitis, but the procedure should not be generally used. During the course of a chronic ulcerative colitis, scarring and deformity of the colon occur constantly. The partial rest which an ileac stoma gives the colon often does not prevent the progress of these deformities: in fact, it occasionally seems to enhance their formation. When the drainage of the lumen of the colon is impossible, a

secondary operation may have to be resorted to for relief of a colonic obstruction. Irrespective of the difficulties encountered when medical treatment is used, routinely ileostomy is still less desirable. After an ileostomy has been performed the colon only obtains partial rest and the patient usually continues to have recurrences of the disease. There also is the handicap caused by the ileac stoma.

The use of serum and vaccine in the treatment of chronic ulcerative colitis has been popularized by Bagen, who uses a diplostreptococcus serum and vaccine. Details of this treatment have been described adequately by him.

All possible measures such as special diets and dietary supplements are used to improve the general health of the patient. In cases in which secondary anemia occurs, blood transfusions should be freely resorted to. Reduced iron may be administered in doses of 5 to 10 grains (0.3 to 0.65 gm.) two or three times daily, but compounds of iron often increase the abdominal cramp and diarrhea. Tincture of iodine in doses of 10 minims (0.76 c.c.) may be given in a glass of water after meals, during alternate weeks. Tincture of opium may be administered in doses of 5 to 10 minims (0.3 to 0.65 c.c.) every six hours for short intervals. Subcutaneous administration of pantopon in doses of $\frac{1}{3}$ grain (20 mg.) may be required for relief of pain. The usual therapeutic measures for the control of diarrhea are almost certain to fail when used in a case of chronic ulcerative colitis. Carbarsone administered in doses of 4 grains (0.24 gm.), twice daily, may produce a great deal of relief.

A patient who has chronic ulcerative colitis should be urged to eat. The following is a good foundation diet:

<i>Breakfast</i>		<i>Dinner or supper</i>	
Cooked cereal.....	1 cup	Meat.....	2 ounces
Cream.....	$\frac{1}{2}$ cup	Potato.....	1 medium sized
Bacon.....	2 strips	Bread.....	1 slice
Egg.....	1	Butter.....	2 squares
Toast.....	1 slice	Bland dessert .	1 serving
Butter.....	2 squares	Cream.....	2 tablespoonfuls
Sugar.....	ad libitum	Coffee or tea, with sugar	

As rapidly as is possible, the daily diet is increased by adding the following foods: half of a ripe banana, orange juice ($\frac{1}{4}$ glass), vegetable purée (4 tablespoonfuls), cream soup,

milk toast, whole milk. The meat servings are increased to 8 ounces daily. As soon as possible, canned peaches, apricots, pears, white cherries, apple sauce, tomato juice and cream and milk are added; the patient should receive three glasses of half cream and half milk daily. Desserts should include custards, junkets, plain rice, tapioca, simple cakes, cookies and plain ice cream. This diet, although outlined for chronic ulcerative colitis, may be used for any chronic diarrhea.

Constipation is usually described as a disturbed intestinal function which results in delayed or incomplete evacuation of the feces. It may be acute or chronic. The common causes of constipation are intrinsic diseases of the colon and extrinsic conditions. The intrinsic diseases of the colon which produce constipation are: inflammation and inflammatory strictures, malignant strictures and tumors, intussusception (polyps), volvulus and strangulation, food poisoning, foreign bodies or materials, ileus and megacolon.

The extrinsic conditions which may produce constipation are: sedentary habits, such as confinement to bed, acute or chronic infections, poisoning by heavy metals, functional disorders and obstruction of the small intestine.

This classification is inadequate but it serves the purpose. In the cases in which the constipation is due to intrinsic disease of the colon, one does not have to pay any particular attention to the symptom, constipation. Diagnosis of the underlying condition is the important problem. Constipation as a symptom of food poisoning occurs most frequently in botulism. In this disease, as in all other types of food poisoning, the constipation may be partially due to the fact that the alimentary canal has been emptied by vomiting and diarrhea. As soon as the patient is able to take food again, treatment will not be necessary.

In a case in which constipation is the result of extrinsic conditions, one should not be loath to institute active treatment for the constipation. The patient who is confined to bed for a long time as the result of a fracture or something of that nature must be treated for constipation and treated adequately. I know of no better laxative than the aromatic fluidextract of cascara sagrada, which should be administered in doses of 1 to 2 drachms (4 to 8 c.c.) at night. For the patient's future

comfort it is just as important to discontinue the administration of the laxative as it is to start it.

Constipation that is the result of acute and chronic infections or poisoning by the heavy metals should be treated in the same manner as the constipation that occurs when a patient is confined to bed in a plaster of paris cast. In selecting a laxative, it is advisable to prescribe the one that the patient prefers. If this is done the results will be gratifying.

It is well to remember that the colon of man does not possess any indispensable digestive function. The only indispensable function of the colon is the maintenance of the continuity of its lumen to the exterior of the body. I have been able to observe patients who have been subjected to a single-barrel ileostomy as a preliminary step to more formidable surgical operations. Under controlled conditions of intake of fluid and food it was possible to compare the composition of the ileac dejecta and urine of these patients with that of normal persons. It was found that the colon does not take part in the digestion of carbohydrates, proteins, or fats. The ileac dejecta contained more salts (chiefly sodium) and water than did feces. The urine of the patients who had an ileac stoma contained less salts (chiefly sodium) than did the urine of the normal persons. The main functions of the colon therefore may be summarized as follows: (1) maintenance of the continuity of the digestive tube to the outside of the body; (2) storage and ejection of alimentary refuse; (3) absorption of salt and water; and (4) excretion, mostly of mucus, which acts as a lubricant. Dispensing with all these functions, by extirpation of the colon, is still compatible with health.

As a result of clinical experience, some authors have expressed the opinion that in some way the function of the colon changes when a person reaches adolescence and again when he reaches the declining years of life. This opinion I believe has originated from the common observation of two facts: (1) that constipation may become more obstinate as the person grows older, and (2) that the diseases of the colon which commonly occur in childhood generally are not those commonly present in the aged. The increasing constipation which often occurs as a person grows older is probably not due to a change in the functions of the colon *per se*, but is related to a decrease

in general muscular tone and sedentary habits. This type of constipation should be treated with laxatives.

That there are so-called age groups in which different diseases of the colon occur is of considerable practical importance; however, the occurrence of these diseases at certain ages is probably not directly related to change in functions of the colon. There is little scientific proof of the widespread belief that toxins are absorbed from the colon. However, this is still a debatable question as anyone will receive a feeling of exhilaration after the action of a good laxative, but I do not know why this is true.

As a concluding remark, I believe that two mistakes may be made in the diagnosis and treatment of diseases of the colon: (1) to allow serious significant symptoms of diseases of the colon to pass unnoticed under the all-inclusive diagnosis of "intestinal flu," and (2) polyps in the rectum and colon should always be removed. Nothing is to be gained by "watching" them. During the period of watching an uncontrollable carcinoma often develops.



THE ASSOCIATION OF CHRONIC ULCERATIVE COLITIS (COLITIS GRAVIS) WITH HEPATIC INSUFFICIENCY: REPORT OF FOUR CASES

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It has long been recognized that infectious processes within the abdomen not infrequently involve the liver secondarily. Appendicitis, pelvic abscesses, umbilical abscesses, infections of the gallbladder and common bile duct, perforated peptic ulcer, gastric carcinoma, malignant disease of the pancreas, malignant disease of the colon, pancreatic suppuration, and diverticulitis of the sigmoid colon have been known to lead to the development of suppurative thromboses of the portal vein and its tributaries and in turn to the formation of multiple hepatic abscesses. Acute appendicitis, acute gastro-enteritis, and acute cholecystitis, even without associated disease of the common bile duct, likewise may cause hepatitis and jaundice. It has not been surprising to find that chronic ulcerative colitis, a much more prolonged and at times fully as acute an infectious process as many of these diseases, likewise has been responsible for infections of the hepatic parenchyma. Such complications, however, seem to be rare. Lansbury and Borgen have reported a case in which chronic ulcerative colitis was complicated by multiple hepatic abscesses. He has also mentioned a case in which the condition was diagnosed Banti's disease and biliary cirrhosis. With the possible exception of this last case, we have been unable to find a single instance of hepatitis and jaundice complicating chronic ulcerative colitis similar to the following four cases that we have observed recently.

REPORT OF CASES

Case I.—A woman, aged sixty-one years, came to the Clinic because of increasing brownish discoloration of the skin and a troublesome pruritus. She had enjoyed good health except for a mild influenzal infection in 1918. Twelve

years before she came to the Clinic multiple joints had become painful and swollen. This arthritic condition had disappeared without residue five years after onset. Seven years prior to her admission to the Clinic, severe bloody diarrhea had developed. As many as twelve stools had been passed daily. This had lasted for a few weeks and then had improved spontaneously. In the interim she had continued to have two or three semiformal stools each day. Some of these stools had been blood streaked but she never had had a return of the severe diarrhea which had been present at the onset.

Four years before the patient came to the Clinic she had noticed a slight generalized brownish discoloration of the skin which had been most marked over the face and arms and had been associated with mild pruritus. The discoloration slowly had increased in intensity.

Physical examination revealed that the brownish discoloration of the skin was generalized over the entire body. There were numerous factitious excoriations. The scleras were not icteric. Examination of the heart and lungs did not reveal any abnormality; the abdomen was soft, and the firm, smooth, rounded edge of the liver could be felt extending 5 cm. below the costal margin during complete exhalation. The spleen could be easily felt at the left costal margin. The urine was normal and the Wassermann reaction on the blood was negative. The concentration of hemoglobin was 12.1 gm. per 100 c.c. of blood. The erythrocyte count was 4,600,000 per cubic millimeter of blood; there was no morphologic abnormality of the formed elements of the blood. There was 1.4 mg. of bilirubin in each 100 c.c. of blood serum, showing a direct van den Bergh test. The bromsulphalein test of liver function revealed dye retention, grade 3. Roentgenologic examination of the colon by the aid of a barium enema disclosed diffuse involvement of the entire colon, which was typical of chronic ulcerative colitis, and two small polypoid lesions. Direct visualization of the rectal mucosa with the sigmoidoscope showed a granular mucosa which bled easily as a result of slight trauma. It was typical of chronic ulcerative colitis of low grade. The diplostreptococcus of chronic ulcerative colitis could not be isolated.

Comment on case I. It is of interest to note that the first clinical manifestations of the chronic hepatitis with splenomegaly appeared three years after development of symptoms of chronic ulcerative colitis.

Case II.—A woman, aged fifty-three, came to the Clinic because of recurrent intermittent attacks of jaundice which had been present for three years, and which recently had been accompanied by diffuse soreness in the upper part of the abdomen. The patient had never been robust and she had had spells of diarrhea as long as she could remember. During the spells of diarrhea, which often had lasted as long as a week, as many as fifteen watery stools, many of which were blood streaked, sometimes had been passed in twenty-four hours.

Twelve years prior to her admission to the Clinic, she had experienced a sudden colicky pain, which had been situated in the right upper quadrant of the abdomen and had extended into the back. This had been followed by a

mild degree of icterus. Cholecystectomy had been performed and a stone had been removed from the common bile duct. The patient had made an uneventful recovery and had remained well for eight years, except for recurrent mild exacerbations of diarrhea. Three years before the patient came to the Clinic she had had a severe attack of diarrhea, which had been associated with watery, blood streaked stools and mild icterus. Proctoscopic examination at that time had revealed that the rectal mucosa was granular and bled easily. In the interim, she had experienced persistent malaise and had had three distinct attacks which had come on with chills and fever, and had been followed by diarrhea which had lasted several days. There also had been definite icterus, and moderate discomfort in the upper part of the abdomen. The whole episode usually had subsided completely within three weeks.

Physical examination revealed that the heart and lungs were normal. The edge of the liver was smooth, rounded, and firm; it projected 5 cm. below the costal margin. The spleen was not palpable. The Wassermann reaction on the blood was negative; the concentration of hemoglobin was 14.5 gm. per 100 c.c. of blood and there was evidence of macrocytosis. The concentration of bilirubin in the serum was 2.7 mg. per 100 c.c.; the van den Berg test was direct. Proctoscopic examination revealed that the rectal mucosa was normal for a distance of 24 cm. from the anus. Because the icterus was the most significant feature, because of the history of the previous occurrence of a stone in the common bile duct, and because of distress in the upper part of the abdomen and the attacks of diarrhea and jaundice, the most likely diagnosis seemed to be a recurrent stone in the common bile duct, cholangitis, hepatitis, and pancreatitis.

Exploratory laparotomy revealed a moderate grade of hepatitis. The common bile duct was small in caliber; it did not contain any stones and it was not obstructed. The convalescence was uneventful and the patient was dismissed from the hospital on the seventeenth day after the operation.

Two weeks after her dismissal from the hospital the patient had a chill which was followed by fever and exacerbation of the diarrhea and jaundice. She was again sent to the hospital for observation. About six watery stools were passed each day. Repeated microscopic examination of the stools did not reveal anything of interest except the presence of *Endamoeba coli*. The diplo-streptococcus of chronic ulcerative colitis was isolated from the stools by culture and a vaccine was prepared. The concentration of bilirubin in the serum was 7.5 mg. for each 100 c.c. Analysis of the gastric contents after stimulation with histamine revealed achlorhydria. A gram-negative bacillus was isolated from the bile which was obtained by duodenal drainage. The acute manifestations rapidly subsided and, when it seemed advisable, roentgenologic examination of the gastro-intestinal tract was carried out. Roentgenograms of the colon revealed typical lesions of chronic ulcerative colitis which involved the colon proximal to the splenic flexure.

The patient was advised to follow the regimen employed in the treatment of chronic ulcerative colitis. This consisted of a bland diet, the administration of dilute hydrochloric acid by mouth, and the administration of 10 minims (0.6 gm.) of tincture of iodine twice a day on alternate weeks. The patient received injections of vaccine prepared from the streptococcus isolated from

the stools. She improved rapidly and two months after her return home she reported that there had been no recurrence of jaundice or diarrhea.

Comment on case II. The sequence of events in this case seems to have been: first, the onset of chronic ulcerative colitis in the early years of life; second, the development of cholecystic disease, at the age of forty-one years, which was completely cured by appropriate surgical treatment, and finally, the appearance of jaundice, chills and fever with each exacerbation of the diarrhea. Exploratory laparotomy excluded disease of the common bile duct as the cause of the jaundice, chills, and fever. The simultaneous exacerbation of hepatitis and chronic ulcerative colitis indicates a close relationship between the two conditions.

Case III.—A white laborer, aged thirty-one years and of good habits, came to the Clinic because of intractable jaundice. For at least twelve years he had been troubled by attacks of bloody diarrhea. At the onset, this condition had been severe, and he frequently had had attacks of diarrhea which had lasted several weeks. He had had as high as twelve bloody stools in twenty-four hours and he often had been severely prostrated. Ten years prior to his admission to the Clinic, he had suffered so much from chronic loss of blood incident to his diarrhea that the concentration of hemoglobin in the blood had become as low as 40 per cent. While he had been in good health thereafter, he had continued to have five or more partially formed stools daily.

Five years before the patient came to the Clinic he first had become aware of mild icterus; this had been noticeable only during the winter months and had not caused any concern. Six months before he came to the Clinic the icterus became much more intense than it had been, and acquaintances had begun to remark about his color. At the same time, he had noted acholic stools, highly colored urine, and failure of endurance.

Physical examination revealed that the skin was deeply icteric. The icterus accentuated the vivid white patches of an associated vitiligo. The patient did not appear ill and said that he felt full of vim. His lungs and heart were normal. The liver was enlarged and its firm, rounded edge could be palpated 5 cm. below the costal arch. The spleen could be palpated easily. The blood pressure, pulse rate, and temperature were normal. Urinalysis revealed albuminuria, grade 2, some casts, and an occasional erythrocyte. The concentration of hemoglobin was 15.9 gm. per 100 c.c. of blood, and there were 4,440,000 erythrocytes in each cubic millimeter of blood. Examination of blood smears revealed marked macrocytosis and a shift of the neutrophils to the right. The Wassermann reaction on the blood was negative. The concentration of bilirubin in the serum was 12 mg. per 100 c.c.; the van den Bergh test was direct. The hepatic function was surprisingly good; the liver synthesized 4.86 gm. of hippuric acid in two hours and the result of the galactose tolerance test was normal. Analysis of the gastric contents after the administration of an Ewald

st meal revealed achlorhydria. Duodenal drainage disclosed a thin, greenish type of bile, from which the *Streptococcus faecalis* was isolated by culture. The diplostreptococcus of chronic ulcerative colitis was isolated from the feces by culture. Roentgenologic examination of the thorax, stomach, and small bowel did not disclose any abnormality, but roentgenologic examination of the colon revealed slight mucosal changes throughout its entirety, which were suggestive of chronic ulcerative colitis, of grade 2. The patient was dismissed after he had been told that he had chronic hepatitis and chronic ulcerative colitis. He was instructed to take a bland, high-carbohydrate diet, decholin tablets, and a vaccine prepared from the diplostreptococcus isolated from his stool. Six months after his dismissal from the Clinic, he reported that the jaundice was unchanged but that he felt well. In the interim, he had experienced transient severe exacerbation of all the previous symptoms. These exacerbations had lasted for several weeks and had been preceded by mild respiratory infection.

Comment on case III. In this case, a long continued chronic ulcerative colitis also was complicated by the development of a chronic hepatitis with splenomegaly. Exacerbations of both conditions occurred simultaneously.

Case IV.—A man, aged forty-four years, came to the Clinic because of unabating jaundice which had been present for five years. Five years prior to his admission to the Clinic, he had contracted a mild respiratory infection which was attended by an unusual degree of exhaustion and followed by persistent, low-grade fever. One month later he had noted the first slight icteric tint of his skin. Two months following the onset of jaundice he had experienced mild diarrhea which had been characterized by watery, blood streaked stools. During the past five years before the patient came to the Clinic, he never had been free of jaundice or diarrhea. These two conditions had seemed to parallel each other; an exacerbation of his diarrhea had been attended by a deepening of the jaundice. The more severe attacks of jaundice and diarrhea usually had lasted two weeks. The maximal number of stools had been twelve in twenty-four hours; some of the stools had consisted almost entirely of blood. He had suffered from malaise, and had lost weight and strength.

Examination revealed moderate icterus. His blood pressure, temperature, and pulse rate were normal. The edge of the liver could be felt very easily; it was rounded and firm and extended 6 cm. below the costal arch. The spleen was enlarged. Except for varicosities of the lower extremities, physical examination was essentially negative. Urinalysis revealed albuminuria, graded 2, on the basis of 4, and a trace of bile. The Wassermann reaction on the blood was negative. There was marked anemia; the concentration of hemoglobin was 2.63 gm. per 100 c.c. of blood, and there were 2,630,000 erythrocytes in each cubic millimeter of blood. Morphologic study of the blood showed definite macrocytosis. The value for the urea was 20 mg. per 100 c.c. of blood; that for the cholesterol was 126 mg. per 100 c.c. of plasma, and that for the protein was 9.9 gm. per 100 c.c. of serum. The concentration of bilirubin in the

serum was 7 mg. per 100 c.c.; the van den Bergh test was direct. The results of the hippuric acid and galactose tolerance tests of hepatic function were within normal limits; 3.1 gm. of hippuric acid were excreted in two hours. No parasites were found in several stools tested. Duodenal drainage yielded bile. Analysis of the gastric contents was not done since several analyses which had been done elsewhere had revealed achlorhydria. Roentgenologic examination of the thorax, stomach, gallbladder, and colon did not disclose any abnormality. Proctoscopic examination revealed that the mucous membrane of the rectosigmoid was granular and prone to bleed on the slightest trauma. It was reported typical of chronic ulcerative colitis of low grade.

A diagnosis of chronic hepatitis with splenomegaly and chronic ulcerative colitis was made. In view of the prolonged jaundice, the exacerbations, and the progressive characteristics, exploratory laparotomy was advised to exclude a lesion of the common bile duct. Exploration was performed elsewhere and the diagnosis of chronic hepatitis was confirmed by biopsy. No anatomic obstruction of the common bile duct was found. He is now taking liver extract parenterally, dilute hydrochloric acid by mouth, stock ulcerative colitis vaccine, and a high carbohydrate type of diet. In a recent letter he reported that his condition was essentially unaltered; he still suffers episodic exacerbations of icterus and diarrhea.

Comment on case IV. In this case, the sequence of events is slightly different from that in the previous three cases. The respiratory infection was followed by the clinical manifestations of hepatitis and only two months later by those of colitis. The occurrence of the disease of the liver was almost simultaneous with the occurrence of the chronic ulcerative colitis and both diseases seem to have been the result of the same infectious process. As in the previous cases, the chronic ulcerative colitis was mild and exacerbations of both diseases were simultaneous.

SUMMARY

In all four cases the outstanding features of the ulcerative colitis were the long-standing nature of the disease, the low grade activity of the process, and the minimal anatomic deformity of the colon. In cases I, II, and III, the colitis preceded involvement of the liver; in cases II and III, diarrhea antedated the first suggestion of hepatic damage by many years. In case IV, the hepatic disease and the colitis developed within a relatively short time of each other. In each case, a close link between the disease of the hepatic parenchyma and the colitis was suggested by the simultaneous increase in the severity of each disease.

In cases I, II, and III, the chronic ulcerative colitis appears to have been responsible for the development of the hepatitis. Such an assumption is not an illogical one inasmuch as other infections in the abdomen are known to involve the liver secondarily. The infection may follow at least three pathways. In cases of suppurative thrombosis of the portal vein the pathway of the infection is obviously by this vein. In a case reported by Bargen, the infection apparently reached the liver in this manner. Even when suppurative thrombosis of the portal vein is not present it is still possible that bacteria may reach the liver by means of the portal vein. The infection may also reach the liver by spreading up the bowel, finally involving the duodenum and common bile duct and producing a cholangitis with secondary hepatitis. Finally, the infectious process in the bowel may first produce a chronic infectious splenomegaly, the liver being affected secondarily. Bargen and Giffin have described cases in which this condition simulated splenic anemia. They reported seven cases of chronic ulcerative colitis in which splenomegaly developed. In two of the seven cases cirrhosis of the liver is known to have been present; in one of these cases the condition was diagnosed as Banti's disease and biliary cirrhosis. In the cases reported in 1930 by Bargen and Giffin, the authors expressed the opinion that the splenomegaly was an example of infection of the liver and splenomegaly secondary to chronic ulcerative colitis.

The presence of achlorhydria in three of the cases which we have reported might be a point to favor the hypothesis that infection reached the liver by ascending the gastro-intestinal tract. This finding may be significant in view of the work of Ricen, Sears and Downing, which seems to prove that the state of the gastric acidity has a large bearing on the bacterial flora of the duodenum. They made a statistical analysis of a large series of cases and concluded that the duodenal content of persons who have a normal gastric secretion is sterile except for the presence of rare organisms which have aciduric cultural characteristics. On the other hand, the duodenal content of patients who had achlorhydria was rich in bacterial flora of different types, many of which possessed hemolytic properties. The organisms which these workers isolated from the duodenal content of patients who had achlorhydria in-

cluded hemolytic streptococci, hemolytic staphylococci, *Streptococcus mitior*, *Diplococcus pneumoniae*, *Escherichia coli*, and *Alcaligenes faecalis*. In the present series of cases, *Streptococcus faecalis* was isolated from the duodenal content in case III and a gram-negative bacillus was isolated from the duodenal content in case II. It is possible that achlorhydria conditioned the success of the ascending infection in these cases.

Chronic ulcerative colitis may follow rather than precede the development of disease of the liver. It seems to have done so in case IV. There seems to be little doubt that the same infectious process was responsible for the development of both conditions. In other cases, the nature of the association is not clear, and it may have been one of chance. Such may have been the circumstance in case I in the report of Saccone and Repetto. Chronic ulcerative colitis developed in the course of what appears to have been, judging from the history given, obstructive jaundice which resulted from a stone in the common bile duct and which was secondary to biliary cirrhosis. These authors reported the case in support of theories advanced by Popovici that hepatic insufficiency (defined as a functional rather than organic disorder of the hepatic parenchyma) conditions the bowel for the development of chronic ulcerative colitis. It seems much more likely that if there was any connection between the two diseases in this case the malnutrition of the patient had so reduced the resistance to infection that chronic ulcerative colitis ensued.

In three cases in the present series, the chronic hepatitis seems to have developed long after the chronic ulcerative colitis appeared. In the fourth case, chronic ulcerative colitis and chronic hepatitis appeared almost simultaneously. The association of the two diseases seems to us to be more than one of chance.

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MEDICAL ASPECTS OF CHRONIC SINUSITIS

HAROLD I. LILLIE

PHYSICIANS have been faced with the problem of treatment of chronic sinusitis throughout the ages, as examination of skulls of ancient civilizations has revealed. During the past quarter century much prominence has been given to the disease through many channels, especially since the advent of radio broadcasts, those responsible for some of which have chosen to advertise certain nostrums. Very inaccurate statements, also, have been made about the disease by physicians whose information has been inadequate. Much misinformation has been disseminated through semi-ethical channels. Lay persons have, for the most part, accepted such information as authentic. These conditions have caused the public to become "sinus disease conscious." It might be added, too, that not only the public has become sinus disease conscious but many physicians are prone to interpret for the patients certain symptoms referable to the head as being attributable to sinus disease. There is nothing mysterious or mystical about disease of the paranasal sinuses. There is no reason why the generally prevalent idea that "once a sinus disease, always a sinus disease" should exist if the function, physiology and pathology, relative to the sinuses were more widely known and if well directed therapeutic measures directed against disease of them were better understood.

As a background for this discussion, it is essential to consider briefly certain anatomic and embryologic aspects of the paranasal sinuses and the physiology of the nose and paranasal sinuses. Pathologic and etiologic aspects will be dealt with more comprehensively.

ANATOMY AND DEVELOPMENT OF PARANASAL SINUSES

From the anatomic standpoint it can be said that there are four paired paranasal sinuses: the ethmoid, maxillary, frontal and sphenoid. The ethmoid sinus can be considered the central one as it lies lateral to the middle turbinate, in the lateral

nasal wall. Above it lies the frontal sinus, which is really a projection of the ethmoid sinus between the layers of the frontal bone. Beyond and below it, in the superior maxilla, is located the maxillary sinus. This is present in a rudimentary form at birth. The sphenoid sinus, situated behind the nose, in the body of the sphenoid bone, does not develop until later in childhood. Its maximal development is said to be present after the adolescent period. The development of the paranasal sinuses may not be symmetrical or they may completely fail to develop. In the developmental process separate sinuses within a sinus may occur. All of the paranasal sinuses communicate with the interior at the nose. The maxillary, ethmoid and frontal sinuses empty into the nose beneath the middle turbinate, in the middle meatus, in a slit-like groove called the "hiatus semilunaris." The posterior portion of the ethmoid labyrinth of cells, and the sphenoid sinus, empty high in the postnasal space. Accessory openings for any of the sinuses may be present.

PHYSIOLOGY OF THE NOSE AND PARANASAL SINUSES

The paranasal sinuses are subject to the same diseases that involve the interior of the nose, and for that reason it seems essential to discuss briefly the physiology of the nose. The main function of the nose is to warm, moisten and clean the air before it goes into the lungs. This is accomplished by a complex intranasal structure. The available membranous surface is increased by projection of the turbinate bones from the lateral nasal wall. The nasal interior is lined by a specially constructed mucous membrane, the surface of which is covered by a blanket of mucoserous secretion. Beneath this blanket are the cilia of the columnar epithelial cells that cover the underlying mucous membrane. Beneath the epithelial layer, in the submucosa, many blood spaces and glands are encountered. The membrane is innervated by the sympathetic nerves, coming for the most part from the nasal ganglion. Beneath the submucosa one encounters the periosteal layer and the transition from the submucosa to the periosteal layer is very gradual. The blood supply comes through the bone and breaks up into capillaries and blood spaces, a sinusoidal type of circulation. For the most part the venous drainage is toward the

orbit and toward the pharynx. The membrane lining the paranasal sinuses is very much thinner than the nasal membrane proper. In fact, it is sometimes difficult to distinguish layers except around the region of the natural ostia where a few glandular elements are present. The surface of the membrane within the sinuses is covered with a thin, serous type of secretion. It can be said to be only moist as there is seldom any excessive secretion. The function of the cilia of both the nose and the paranasal sinuses is very important for it has been shown that the cilia are capable of moving a blanket of secretion greatly in excess of what might be supposed. The direction of motion of the cilia in the sinuses is toward the natural openings. The direction of motion of the cilia within the nasal interior is toward the back part of the nose.

The normal secretion of the nose can be considered bactericidal in nature; at least it is bacteriostatic. When it is considered that the nose is the only part of the body that cannot be protected from its environment as other parts of the body can be protected, it must be realized immediately that in order to withstand the effects of environmental changes it must have a wonderfully adaptive functioning mechanism. It is known that the nasal membranes may secrete from a pint (500 c.c.) to a quart (1,000 c.c.) a day, depending on the state of health and the necessity for secreting these amounts. The normal way for animals to clear the nasal passage of any excessive secretion is by hawking it backward into the pharynx, or by sneezing. Man thinks he has improved on nature's way of clearing the nose when he forcibly blows through the nose. Usually, in addition, not content to use just enough force to clear the nostrils, he invariably holds one nostril closed and blows forcibly against the opposite nostril. If the nostril through which he tries to force the air is blocked either by swelling of the mucous membrane or by the formation of polyps or some anatomic abnormality, frequently the force is caused to extend to the middle ears through the eustachian tubes, or to the paranasal sinuses. If infection is present in the nose or nasopharynx, it is at once seen that this is one of the reasons why infection takes place in the middle ears or the paranasal sinuses.

In the functioning of the nasal membrane there is a definite cycle of swelling and retraction. In the process of swelling

the blood spaces are filled and the point is reached at which no more blood can be taken into the blood spaces; gradually then the blood is forced into the glands, and the glands in turn begin to secrete onto the surface; when this occurs the nasal membranes begin to shrink. The cycle is not timed to go through the same phase in each nostril at the same time or there would be a phase in which both nostrils would be closed.

As a result of exposure to climatic conditions, the nasal membranes undergo certain physical changes comparable perhaps to the physical changes that occur in the skin or in any exposed part of the body. If the environment is that of the northwestern or northern section of this country, where the function of the nose is called on to a greater degree, hypertrophy and hyperplasia of the constituent parts of the membrane take place. This may cause certain physical changes in the nasal membrane and, if the natural ostia of the sinuses are small, this natural increase in size may partially or completely block them. As a result of hypertrophy and hyperplasia, later in life secondary atrophy may be present as a natural sequence. In southern climates, where the air is constantly warm, moist and equable, the nasal membrane is not called on to function to the same extent as it would be in the north and, as a result, it remains more or less quiescent and inactive. Those persons whose membranes have undergone physical changes because of exposure to weather, many times may complain of stuffiness and increased secretion and will give a history that if they sojourn in a climate that is warm and dry, they are entirely relieved of their subjective symptoms. This is easily explained on the basis of the activity of the nasal membranes.

The physiology of the paranasal sinuses is unknown. All that can be said is that inspiration of air causes a negative pressure within the paranasal sinuses. Expiration causes the pressure to increase. Some observers have felt that in this way the sinuses may act as auxiliaries to the nasal function, as a storage chamber for the warmed air.

PATHOLOGIC AND ETIOLOGIC ASPECTS OF THE NOSE AND PARANASAL SINUSES

Infection in the nose and the adjacent cavities takes place because of some physicochemical change which causes some

loss of function of the vasomotor system. Infection usually takes place in the nasopharynx and spreads by continuity and contiguity to the nose and larynx. The pharyngeal membrane has no such adaptive mechanism as does the nasal membrane. Any organism may cause infection. Certain of them cause certain characteristic conditions but it is known that in association with influenzal infections the paranasal sinuses are more frequently involved than when any other infection is present. In the presence of contagious diseases of children, such as measles, scarlet fever, and so forth, the sinuses are frequently involved.

Evidence of inflammation in the nose and paranasal sinuses is the same as evidence of inflammation elsewhere in the body. Swelling, redness and tenderness are present. If the swelling is intense within the paranasal sinuses it can be expected that there will be considerable discomfort from pressure. These painful subjective symptoms may last during a period of congestion. When increased secretion from the glands begins the symptoms begin to be relieved. It can be said that there are three stages of acute infection within the nose: a period of congestion which lasts anywhere from twenty-four to seventy-two hours, a period of increased serous secretion which may last for several days and a period of mucopurulent discharge which lasts until complete resolution has been established. There is little question but that in all cases of acute rhinitis the sinuses are involved to some extent and the tendency is manifest, if they become involved, to undergo resolution in the manner in which resolution takes place in a nasal infection. However, if resolution of the nasal infection has taken place, and the character of the discharge changes from a mucopurulent to a purulent type, then it can be assumed that there is present an infection of one or more of the paranasal sinuses. However, again the tendency is for resolution to take place under properly directed therapeutic measures. There may be few subjective symptoms other than the need for using several handkerchiefs a day. On the other hand if the subjective symptoms do not improve and there is no increase in the amount of purulent discharge, then one can suspect the presence of closed empyema, owing to the fact that the natural

ostium has been blocked off by the effect of swelling of the membranes.

Chronic sinusitis develops after repeated attacks of acute sinusitis for several reasons: (1) After each inflammatory attack the mucous membrane undergoes another inflammatory infiltration and returns to its normal condition with greater difficulty. (2) The outlets of the infected sinuses become less patent than before because of the thickening of the membrane around the openings. As a result there develop different forms of inflammatory changes: a chronic inflammatory type of change in which, macroscopically, the membrane is edematous, contains true cysts, has undergone diffuse hypertrophy and has given rise to pedunculated polyps; there is marked increase in size of the whole structure. Microscopically it is seen that the mucosa, even to its deepest layers, is edematous and changes of moderate cellular infiltration have taken place beneath the mucosa. There is varying evidence of fibrosis, depending on the reaction of the tissues to the repeated insults of infection. The infection may extend through the periosteum to the bone, at first producing thickening of the periosteum; this may be followed by either the osteoclasts breaking down the bone by taking away the calcium or, if the protective mechanism is stimulated, the osteoblasts deposit bone and produce sclerosis or thickening as a barrier to further extension of the infection. In addition, infection of the bone may result in osteomyelitis from localized abscesses forming along the veins in the cancellous bone. The condition may spread by thrombosis, producing either localized osteomyelitis or diffuse, rapidly spreading osteomyelitis.

SYMPTOMS AND SIGNS OF DISEASE OF THE PARANASAL SINUSES

Symptoms may best be divided under the headings of local symptoms and general symptoms.

Local Symptoms.—Among these symptoms is headache. In the chronic form of sinusitis the headache is not usually acute or well localized but is usually of a diffuse and indefinite character. The headache may be very irregular in relation both to intensity and duration. It may persist for days and then there may be periods of relative freedom from pain. It should be emphasized strongly that the headache does

not constitute a necessary link in the chain of symptoms in chronic inflammatory disease of the paranasal sinuses. Definite purulent sinusitis may be present for years without any headache. The subjective localization of pain in certain regions of the head is not typical of involvement of individual sinuses. In the headache associated with chronic sinusitis there is a certain constancy only when it does not change in position or location. It should be emphasized especially that all headaches are not owing to disease of the sinuses. The rhinologist is frequently confronted with patients who think they have disease of the sinuses because they have headache. Not always is this self-diagnosis dependable.

Discharge of a mucopurulent or purulent character, sometimes fetid, is the most constant and predominating symptom of chronic sinusitis. The discharge may vary in amount considerably. It may present itself at irregular intervals and this would justify the strong suspicion that it was attributable to siphonage from the maxillary sinus. As the maxillary sinus gradually fills, the accumulated material comes to the level of the natural opening of the sinus and siphonage takes place. During an acute exacerbation following an acute infection of the upper part of the respiratory tract there is considerable increase in the amount of discharge. One of the common symptoms of which patients complain is that they use several handkerchiefs a day.

Disturbances of the sense of smell are frequently complained of and they have two possible causes: Either degeneration of the olfactory membrane takes place, owing to the chronic infection, or hypertrophy of the membrane does not permit the air to reach the olfactory cleft. Patients may complain of a fetid odor and this is important. This disagreeable symptom occurs irregularly, or it may be constant, and usually it means that one or another of the paranasal sinuses is involved and that within the sinus the purulent secretion has undergone caseous degeneration.

Patients frequently complain of postnasal discharge and occasionally, because of the tendency of the mucus to cling to the pharyngeal wall and the consequent difficulty in removing it, vomiting results.

General Symptoms.—Fever is scarcely ever a prominent

symptom of chronic sinusitis although, in certain cases, fever of undetermined origin has been found to be attributable to chronic infection of the paranasal sinuses.

Malaise is a common symptom in chronic sinusitis and is attributable to the wearing effect of the symptoms to which reference has been made. In addition, there may be, in certain cases, some absorption which has a deleterious effect on the general bodily economy.

DIAGNOSIS

The diagnosis of chronic sinusitis may be simple or difficult. When the symptoms are strongly suggestive and the physical findings are definite, diagnosis is relatively easy. When the symptoms are indefinite and physical findings are lacking, many observations may need to be made in a given case before the sinuses can be ruled out as a cause of the symptoms. Because the diagnosis of chronic sinusitis is the function of the rhinologist, it does not seem necessary in this discussion to go into great detail about the diagnostic measures.

Roentgen Rays.—The roentgen rays play a very important part in the diagnosis and treatment of chronic sinusitis. Also, roentgen rays can give much false information and the rhinologist should be able himself to interpret the changes that are shown in the roentgenograms. It can be expected that the roentgen rays will show well the anatomy of the sinuses, whether they are symmetrically developed, and their size, shape and position. The two sides should be compared in estimating physical changes. As one's skill improves, small differences which are very important can be made out. That one sinus is shown, on roentgenologic examination, to be dark compared with its fellow, does not mean that the sinus is filled with pus. It merely means that the sinus contains something that does not permit the rays to penetrate it; thus, to say that the roentgenogram gives evidence of the presence of pus, unless a definite fluid level can be made out, is inaccurate. Roentgenologic findings in examination of small sinuses are more difficult accurately to interpret than they are in examination of large sinuses because of the density of the bony walls. It is important to estimate the condition of the mucous membrane and this is sometimes difficult to do. It can be

said in general that roentgenologic examination gives more accurate results for conditions other than infections, such as osteoma and malignancy. It should be emphasized that roentgenograms must not be relied on for accurate diagnosis in a case of disease of the sinuses but they must be taken into consideration along with the history and the physical findings resulting from competent observation in the case.

TREATMENT

The aims of treatment of chronic paranasal sinusitis can be said to be establishment of drainage and ventilation. This occasionally can be accomplished by general treatment of the patient and local treatment within the nose. For the most part, however, it has been shown that treatment of frank chronic sinusitis is essentially surgical. Of the general measures that are important in treatment in a case of chronic sinusitis are the elimination of other diseases by appropriate treatment and the general building up of the protective forces of the body. Many times the condition is attributable to insufficient or inadequate diet and to inadequate rest; these may cause general fatigue and may lower bodily resistance. Many times the disease is owing to the patient's occupation. If these conditions can be corrected by appropriate treatment and hygienic measures, the direct local treatment of the nasal condition is greatly aided.

Local Treatment.—This consists, in part, of application of astringent solutions to the regions of the natural openings. Such solutions cause sufficient shrinking of the nasal membranes to open the natural ostia and permit the discharge from the involved sinuses to escape. If hypertrophy has resulted in closing off the middle meatus, it is best, after thorough cocaineization of the parts, to infract the middle turbinate away from the lateral nasal wall. This permits of more direct and adequate treatment of the middle meatus and the natural ostia. The same obtains for the sphenoidal sinus. If the middle turbinate, because of its contact with the nasal septum, does not permit of inspection of the postnasal wall, then the turbinate may be infracted away from the septum toward the lateral nasal wall. The ostium can be found and canalized and the interior of the sinus can be treated directly by lavage or by

suction. In treatment of the maxillary sinus and frontal sinus it is sometimes possible, because of the size of the natural openings, to treat the interior of the sinus directly, in the same way as that employed for treatment of the sphenoid sinus. A certain percentage of patients who have chronic sinusitis will respond to this treatment and the results will be good over a long period of years. The treatment may of necessity need to be repeated each time the patient has a severe "cold" but the probabilities are that the condition will respond to treatment each time.

Another method of treatment that has been in vogue for a number of years is the Proetz displacement treatment. This is accomplished by placing the patient supine, with the head extended backward in an exaggerated position, so that the eye and the ear are perpendicular to the plane of the body. An astringent substance, such as 0.5 per cent solution of ephedrine sulfate in physiologic solution of sodium chloride is instilled into the nose slowly and is permitted to remain in position for varying lengths of time. The idea is that the solution will seek its own level in the region of the natural ostia of the sinuses, will cause shrinking of the membranes and will flow into the sinuses. This method also has been used for the instillation of opaque media for subsequent roentgenographic examination.

Suction.—General suction applied in the nose has been employed for a good many years. It can be used advisedly or its use can be misdirected. That it has a definite field of application there can be no doubt. After shrinkage of the nasal interior by appropriate astringent solutions, the tube of the suction apparatus may be placed in the nostril and the opposite nostril closed. The nasopharynx may be closed by having the patient say "kay" or, if this is not effective, the patient may be asked to swallow; at the time of the act of swallowing the nasopharynx is closed off. The negative pressure thus produced causes emptying of the paranasal sinuses if the ostia are sufficiently patent. It is evident that this method of treatment can be carried too far and whether the treatment is excessive can be judged only by the individual indications of too strenuous pressure. The method not only relieves the sinus of its content but it produces a hyperemia

of the membrane which is in some measure effective in causing resolution of the disease. The method must be used with circumspection.

Postural drainage has been disappointing in its effect. Also, the inadvisable use by patients of sprays which shrink the interior of the nose, and the use of nasal irrigations which in certain cases produce definite waterlogging of the nasal membranes are mentioned only to be condemned. Many patients have been observed who have for a long period used astringent solutions as sprays, on the advice of their physicians, without any good effect being produced on the underlying disease, but instead new symptoms have been added to the old. Discontinuation of this method of treatment has, in the course of two or three days, caused the nose to assume an entirely different appearance and the patient has been subjectively greatly relieved.

If chronic disease of the paranasal sinuses does not respond to the foregoing methods of general and local treatment, then surgical measures must be considered. Because surgical treatment of disease of the paranasal sinuses is an involved subject, in this discussion it cannot be considered.

DIAGNOSIS OF LESIONS OF THE SPINAL CORD

HENRY W. WOLTMAN

AMONG the diseases most feared are those of the spinal cord. The luckless victim may comfort us with his cheerfulness and courage but our efforts in his behalf are limited distressingly. Sometimes the opportunity for cure exists, but it is usually in disguise and it may be overlooked.

The characteristic disorders of various functional units of the cord may be illustrated by the following case. A man, aged thirty-two years, complained of paralysis of the left arm. Four months previously he had noted an aching type of pain in the left occipital region, which was present on awakening and which gradually disappeared after breakfast. He had become constipated and had found that he could not void until his bladder had become well filled. Three months previously, the left arm had felt heavy and it was necessary that he look carefully at an object when he attempted to pick it up with his left hand; otherwise, the object would escape his fingers. He had become aware of a slipping sound made by his left foot when he walked. One evening to his astonishment he had stepped with the left foot into a scalding hot bath which, when previously tested with the right hand, had seemed to be neither hot nor cold. Subsequently, the right half of the body had tingled constantly. On occasion he had vomited unexpectedly. The story was one of progressive disability, beginning with pain in the left occipital region, followed by vague sphincteric disorders, impairment of joint sensibility in the left hand, left hemiparesis, right hemithermanesthesia and by symptoms which suggested increasing intracranial pressure.

Over the right half of the body below the radicular distribution of the fourth cervical segment there was loss of appreciation of pain and temperature, but appreciation of touch was normal throughout (Fig. 111). Since painful and thermal stim-

uli cross to the opposite side of the cord, loss of these sensations on the right side of the body suggested involvement of the pathways which conduct these forms of sensation, that is, the left lateral spinothalamic tract. Since tactile stimuli ascend partly in the homolateral posterior column and partly in the anterior spinothalamic tract of the opposite side, their preser-

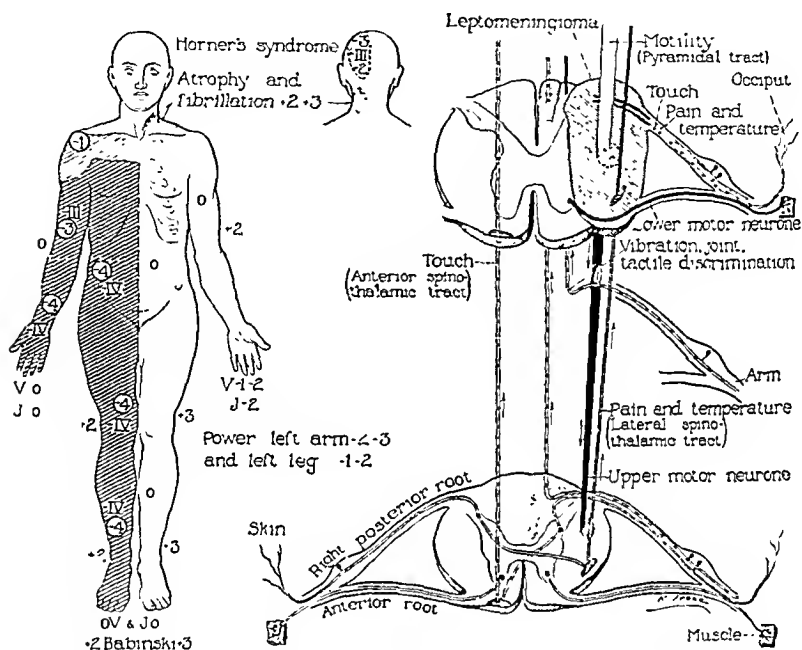


Fig. 111.—Extramedullary intradural tumor on the left side at first and second cervical segments. Intensity of changes is charted on a basis of 0 to plus or minus 4, 0 indicating normal, minus 4 indicating complete absence, plus 4 indicating maximal increase. Arabic figures represent appreciation of touch; encircled Arabic figures, pain; Roman figures, temperature. Injured pathways are represented in solid black.

vation indicated that at least one of these pathways was intact. The left arm and left leg, although they were normal in bulk, were paralyzed and were spastic; increased tendon reflexes and extension of the great toe on plantar stimulation were elicited. This indicated that injury of the left pyramidal tract had occurred. Faulty perception of movements of the joints and of vibration in the left upper extremity indicated that the lesion

involved the lateral aspect (fasciculus cuneatus) of the left posterior column. In other words, the Brown-Séquard syndrome, which is indicative of a lesion affecting one side of the cord, was well developed. The drooping eyelid and the small pupil on the left side, Horner's syndrome, were owing to paralysis of the sympathetic fibers and indicated that a lesion was present at a level not lower than that of the first or second thoracic segment, since no sympathetic fibers subserving these functions leave the cord below this level. The left sternomastoid, trapezius and nuchal muscles were weak, atrophied and fibrillating; this indicated that involvement of lower motor neurons had occurred. Since all these muscles are innervated by cells of the first four cervical segments on the same side, sharper localization became possible. Over the left occipital region in the territory supplied by the posterior root fibers of the second cervical nerve, appreciation not only of pain and temperature but also of touch was lost. These phenomena localized the lesion sharply to the left side, in the region of the first and second cervical segments. Projectile vomiting was probably caused by encroachment of the lesion on the foramen magnum. Since the history indicated that progressive involvement had occurred, tumor was the most likely cause. Subtotal removal of a malignant meningioma was followed by marked but temporary improvement.

COMPRESSION OF THE SPINAL CORD

Recognition of compression of the spinal cord as the cause of disability is of urgent importance since remedial measures, if not delayed unduly, are often productive of excellent results. The cardinal signs are gradual progression of the disability, establishment of a level above which function remains unimpaired, predominantly unilateral involvement and evidences of the presence of subarachnoid block as determined by jugular compression tests in the course of spinal puncture and by elevation of the content of protein in the spinal fluid.

One of the most important causes of compression of the spinal cord is tumor. An accurate history of the case is indispensable. The earliest and commonest complaint is of pain, which is present in approximately 80 per cent of cases. The average duration of this symptom is more than two years. It

is shortest when the tumor is extradural, longer when it is intradural but extramedullary and is longest when it is intramedullary. Pain may be at the site of the tumor; it may be referred to the lower extremities even when the tumor lies high in the canal, but usually it is referred along the distribution of a contiguous posterior root; under such conditions it is known as root pain. It is the peripheral radiation of root pain and its various qualities, such as aching, squeezing or piercing that so frequently suggest disease of the pericardium and pleura; of the biliary, urinary and gastro-intestinal tracts; of the peripheral nerves, and of muscles and bones.

Fortunately, root pain has certain characteristics. It has a segmental distribution; that is, it is distributed lengthwise in the arms and legs and in a circular manner in the trunk. Also, since tumors grow, the pain becomes gradually more intense and adjacent roots become involved; unilateral sciatica becomes bilateral sciatica, and unilateral pain in the trunk has added to it a complementary pain on the opposite side, completing the so-called girdle. Since there are usually no diseased organs at the site of pain, there is, as a rule, no local tenderness. Coughing, sneezing, compression of the jugular veins, or, in short, anything which suddenly increases the pressure of the spinal fluid may aggravate the pain. Root pain habitually causes the patient to awaken at 3 or 4 o'clock in the morning. He discovers that relief can be obtained by walking or by sleeping in a chair. In both of these positions the spine becomes relatively shorter. A helpful test consists of flexing the head sharply on the thorax; this simple maneuver often elicits or accentuates the pain. Explanation is probably to be sought in the resulting traction on the cord and dura and in the increased congestion within the head which displaces the cerebrospinal fluid into the spinal canal. It is important to know precisely the site of the pain, which may be indicated by pencil marks on the patient. The dates of its appearance and its radiation should be recorded. The patient soon may become aware of clumsiness in running or of outright muscular weakness. As a rule, weakness is slowly progressive and is usually owing to injury of the corticospinal pathway, pyramidal tract, or upper motor neuron. The homolateral muscles below the level of the tumor, although they retain their bulk, become

weak and spastic; the tendon reflexes are increased and if the sole of the foot is scratched, extension of the great toe occurs. Inspection of the tips of the patient's shoes may show a decided difference in the amount of wear that has occurred.

Sometimes paralysis is owing to direct injury of the contiguous anterior horn cells or of the ventral roots, which together constitute the lower motor neuron. If this occurs, the segmentally related muscles fibrillate and become atrophied, weak, and toneless and their reflexes become correspondingly feeble. By consultation of suitable charts, the level of the nerve cells that innervate muscles so paralyzed can be determined. This type of paralysis is the best of localizing signs.

Some patients collapse suddenly, arise and wonder why they fell; often this is associated with the presence of dumb-bell-shaped tumors which lie partly within and partly outside the spinal canal and may be owing to transitory compression of the cord. Other patients who become suddenly weak may have suffered from hemorrhage or from softening of the cord incident to the tumor.

Subjective sensory disturbances appear sooner or later. The patient may complain that his underwear is unbearably irritating; the feet may be described as "dizzy"; the limbs may move to unanticipated positions; there may be burning, tingling, or a sensation of woodenness. These disturbances result from interference with the posterior roots or with the sensory tracts in the cord. Disturbances in the sphincteric and sexual functions may add to the discomfort of the patient. These complaints do not vary greatly with the situation of the tumor.

Following spinal puncture, aggravation of all symptoms is a common occurrence; neurologic examination may make it possible to establish the level of disturbance with ease when it was impossible to do so before.

Tumors in the upper end of the spinal canal may present certain peculiar features. The exposed situation of the decussating pyramidal tracts on the anterior aspect of the cord, in the presence of a tumor, may result in quadriplegia unaccompanied by disturbance of sensation. The disturbances of sensation associated with tumors situated high in the cervical region may be limited to the lower extremities or may fluctuate

from time to time and from place to place, probably because the canal is relatively large and its contents mobile, thus permitting readjustment of the various structures. Involvement of the descending root of the fifth nerve may result in pain referred to the face and in anesthesia for pain and temperature over certain areas of the face, particularly over the forehead. The proximity of the tumor to the foramen magnum may bring about signs of tumor of the brain, such as projectile vomiting and choked disks.

If tumors occur in the lower end of the spinal canal, the long intraspinal course of the lumbar and sacral nerves makes it extremely difficult to determine the exact level of disturbance and whether there is a tumor of the cord, of the cauda, or of the sacrum. Neurologic data may be the same in all cases. Data obtained by spinal puncture, roentgenologic examination, and by examination through the rectum usually obviate serious blunders.

The spinal fluid is practically without circulation. The slightest change in pressure at any site, however, is transmitted throughout the remainder of the fluid. Because of the limited space in the spinal canal, eventually a growing tumor interrupts the continuity of the fluid in the subarachnoid space.

In most cases such a blocking can be demonstrated by a simple maneuver described by Queckenstedt in 1916. When the spinal puncture needle and the attached manometer are in place, pressure on the jugular veins normally causes a rise in the column of fluid in the manometer, owing to filling of the intracranial venous channels, with consequent displacement of cerebrospinal fluid along the spinal subarachnoid space, through the needle and into the manometer. Release of the pressure on the veins results in prompt fall of the column of fluid in the manometer owing to return of the fluid to its previous hydrostatic condition. If the pathway of the fluid in the canal is obstructed by a tumor, the degree of interference is registered by the column of fluid in the manometer. Should the tumor lie low in the canal, the needle may pierce the tumor and a dry tap may result, or the needle may enter the canal above the tumor. When this occurs, a block sometimes can be demonstrated by injection of a saline solution into the epidural

space by way of the sacral hiatus and by noting the result produced in the manometer.

The fluid obtained from the canal below the site of a tumor is often yellow. The fluid above the site of the tumor can also be yellow, but usually it is of a lighter color than that of the fluid obtained from the canal below the lesion. The concentration of globulin of the fluid almost invariably is increased. The total concentration of protein of the fluid in cases of tumor is usually high, more than 45 mg. per cent. Removal of 7 c.c. of fluid normally results in lowering the basal pressure of fluid about 50 per cent; if the fluid is loculated, the fall in pressure is usually great and the amount of fluid obtainable may be small.

Roentgenographic examination occasionally reveals erosion of bone produced by a tumor, or may reveal the presence of even a calcified tumor. The commonest site of early erosion is at the pedicles. Roentgenography is also one of the most certain methods of excluding metastatic tumors and other diseases of the bone. Introduction of an opaque medium, such as iodized oil, into the subarachnoid space through cisternal or lumbar puncture is becoming more helpful as experience with its use increases. Resulting irritation can be severe, particularly if an inflammatory lesion is already present. Oil should not be used unless it is urgently indicated, or if performance of laminectomy seems probable from the nature of the case, since removal of large amounts of oil except by laminectomy is not easy. When it becomes necessary to use such an oil the amount introduced should be sufficient to be helpful and to prevent the roentgenologist from making wrong deductions.

Intramedullary Tumors; Syringomyelia.—Just what causes syringomyelia is unknown but its relationship to intramedullary tumors is close, since about half of the intramedullary tumors that occur are associated with syringomyelia. The latter disease, of course, may appear independently. The cardinal features of syringomyelia are a long course, dissociated sensory disturbances of a waistcoat distribution, curvature of the spine and a succulent appearance and texture of the hands and feet owing to involvement of visceral pathways. Owing to frequent interruption of the fibers subserving appreciation of pain and temperature at the decussation anterior to

the spinal canal, there is often a girdle or a waistcoat distribution of thermanesthesia and analgesia in the presence of unimpaired tactile sensibility. The extent, position and character of such sensory, motor and visceral disorders vary enormously and depend on the multidirectional disposition of syringomyelic cavitation and gliosis in the cord. To these manifestations may be added tract symptoms and signs below the level of the lesion. Treatment is restricted largely to surgical drainage of the distended cord and to roentgen therapy. The former is usually indicated when spinal puncture discloses blockage of the subarachnoid pathways; the results may be most gratifying, but it would be foolhardy to prognosticate the amount of benefit, if any, that the patient may derive from operation. The results of roentgen therapy are none too good in most instances but, according to present knowledge, it represents a justifiable attempt to help the patient.

Hypertrophic Pachymeningitis; Hypertrophic Osteitis of the Spine.—Hypertrophic pachymeningitis can be associated with enormous overgrowth of tissue which compresses all structures in its path. This process is situated more commonly in the cervical region. Strangulation of the nerve roots causes segmentally distributed pain, paralysis and, to a less extent, impairment of sensation and strangulation of the spinal cord, a sensory-motor paraplegia. Although the usual cause is syphilis, hypertrophic pachymeningitis now is seen rarely.

Just as hypertrophy of the dura occurs, so may there be hypertrophic osteitis of the spine with resulting involvement of nerve roots and cord. Presumably this disorder is the result of infection. Information derived from roentgenologic examination is often meager.

Fracture of the Spine.—The history of the onset usually suggests the nature of the lesion. The junctures of relatively mobile segments with the more fixed segments of the spinal column are the commonest sites of such injury. Usually the force is applied to the body of a vertebra, the top of which finally gives way. When the atlas is fractured the line of separation of the fragments usually passes through one or both sides of its posterior arch which is weakened by the grooves along which the vertebral arteries pass.

The spinal column may be fractured without production of

neurologic symptoms or signs. Occasionally the nerve roots emerging at the site of the fracture bear the full brunt of the trauma to the nervous system. Unfortunately, injury to the cord occurs in about a third of the cases of fracture of the spinal column; it is the gravest of neurologic complications. The force of the injury itself may cause intramedullary disintegration and hemorrhage without compression of the substance of the cord or root by bone. There may be an associated shock-like state which may last four or five weeks and which represents the part of the disability from which recovery occurs most readily. The sphincters are usually in a state of contraction for a variable length of time following the injury. Subsequently, the sphincters may relax and may remain relaxed, or a state of periodic involuntary action may ensue. Persistent priapism commonly is associated with cervical lesions; conception and normal but painless parturition may occur.

Occasionally paraplegias develop slowly following injuries of the spinal column with or without involvement of the cord at the time of the injury. This delayed paralysis may be owing to meningomyelitis, to spinal gliosis or to circumscribed cystic meningitis. Rarely, tumors form at the site of the previous injury but the exact relationship is not well understood.

In view of the serious outlook, temptation to explore is great; however, injury to the cord is comparable with the results of dropping a glass on the floor; the damage is almost immediate and is often irreparable. If roentgenograms give evidence of such marked overlapping of the bone that complete shearing of the cord is a foregone conclusion, operation hardly can be of help; if the vertebrae are in fairly satisfactory alignment and if spinal puncture gives no evidence of a block, operation is hardly necessary; if the vertebrae are in satisfactory alignment but a block is present, laminectomy may be advised. The possibility of assisting nature by surgical repair is decidedly better in purely caudal injuries. In all cases of fracture of the spine utmost care must be taken that the damage is not aggravated by handling the patient. It is needless to say that the urinary tract should receive meticulous attention; the bowels should be cared for routinely and the skin should be protected by use of smooth, soft bedding and by frequent change of the patient's position. In lieu of an air or water

mattress, a sheep's pelt serves admirably and has the advantages of cheapness and stability.

A type of injury to the cord that may escape proper evaluation is spontaneous hyperemic atlo-axoid dislocation. Usually such a dislocation consists of the atlas moving forward on the axis and, when the dislocation is marked, either the odontoid process or the transverse ligament gives way. Since the pyramidal decussation lies immediately behind the odontoid process, the former may be impinged on and paralysis without loss of sensation may result; when this occurs, paralysis of the arms commonly is more marked than is paralysis of the legs. In cases of graver injury, sensation also may be affected and sudden death, through compression of the medulla, is a common occurrence.

The usual cause of dislocation is trauma, particularly the type in which falls on the head are sustained. Sudden muscular strains without a direct blow may suffice to cause such dislocation. Traumatic dislocations usually present little difficulty in diagnosis. Nontraumatic dislocations can be misleading and can simulate cervical arthritis, pharyngeal abscess, meningitis, encephalitis, cerebellar tumor, syringomyelia, bulbar palsy and myasthenia gravis. Infections that involve the head or neck may be followed by gradual atlo-axoid luxations and together constitute a distinct clinical syndrome referred to as "Grisel's disease," "occipito-atlantoid torticollis," or "torticollis nasopharyngien."

Jones^{3,4} called attention to four prominent features of this condition. First, it is peculiar to children; second, it follows inflammation anywhere in the upper cervical region, such as pharyngitis, tonsillitis, mastoiditis; third, there is a latent period of seven to ten days between the time when infection occurs and the time when dislocation becomes evident; and fourth, that part of the arch of the atlas which is nearest the region of infection, usually the anterior part, becomes decalcified. Jones offered the explanation that congestion leads to decalcification; this in turn loosens the attachments of the ligaments and static conditions accomplish dislocation. Grisel^{1,2} attributed dislocation to relaxation of the ligaments. Treatment is by traction or by application of a collar and, sometimes, by decompression.

INFECTION

Infection may reach the cord by way of the blood stream, the nerves and their sheaths, the subarachnoid space and by extension through contiguous tissues. Closure of vessels may result in myelomalacia and the common expression of infection clinically as transverse myelitis is often owing to this type of incident. Meningitis may involve the cord directly, resulting in meningomyelitis or the effect on the cord may be less direct, namely, by way of meningoradiculitis with resultant secondary degeneration of the spinal cord, particularly of the posterior columns.

Syphilis.—Syphilis is an important and common cause of degeneration of the posterior columns of the cord. The full-blown picture of tabes is now rare in comparison with its almost commonplace incidence some years ago.

Lightning pains are almost pathognomonic of parenchymatous neurosyphilis and are encountered but rarely in cases of diabetic neuritis, syringomyelia and among apparently healthy persons. Typical lightning pains are sharp, short, spot-like more often than streaking (a negro who had tabes, aptly compared them with "lightnin' bugs"); they are severe or mild, appear in showers, often in the same spot during the same shower; are present usually in the lower extremities, are not limited to the region of the joints and may leave the skin hypersensitive to light touch, but not to heavy pressure.

Crises also are strongly suggestive of neurosyphilis, but may be associated with migraine or with angioneurotic edema; they may be familial or of unknown origin. They occur in various organs of the body such as the eyes, the larynx and the rectum but the commonest site of crises is the abdomen. The onset is usually sudden, usually there is either pain or vomiting, or both; extreme nausea and sialorrhea; the pain is situated usually near the midline and is symmetrical in distribution; the pain has been described as dull or sharp; aching, cramping, squeezing, or burning; mild or excruciating; it can last from a few hours to several days, or, rarely, may be continuous. Crises usually terminate suddenly and, unless there is present some complication, no intercurrent abdominal symptoms occur. They tend to recur at widely varying intervals. Tenderness on deep pressure is not elicited but there may be

hypersensitivity to the lightest touch. Usually, objective evidence of syphilis exists.

The characteristic signs of parenchymatous neurosyphilis include the Argyll Robertson pupil; absence of patellar or Achilles tendon reflexes (which merely indicates that interruption of the reflex arc has occurred and is not indicative of tabes); although superficial sensibility is preserved fairly well, there is absence of pain on pinching the calf; delay in appreciation of painful stimuli, readily demonstrated by pricking the foot with a pin, at which time the patient, describing the sensation, first will say "dull" and then, correcting himself, will say "sharp"; and impaired sensibility over the thoracic zone.

Meningomyelitis.—Troublesome diagnostic and therapeutic problems may be presented by meningomyelitis. Often there is a history of previous injury to the back and the extent to which infection contributes to production of the ultimate malady remains obscure. When this disorder is slowly progressive it simulates compression of the cord. Usually, however, the disturbance is fairly symmetrical. On comparing this condition with that of compression of the cord there occurs little dissociation with involvement of the sensory pathways, the upper level of sensory disturbance is less sharply defined, and the loculation syndrome (xanthochromia and elevation of the content of protein of the spinal fluid) is less prominent and behavior of lipiodol is of a different order. Mechanical separation of the adhesions may be helpful.

Abscess.—Abscess of the cord is an uncommon occurrence. Patients of any age, especially males, may be affected. Causes to which abscess formation has been ascribed include diseases of the spine, such as fracture, Pott's disease, and carcinoma; diseases of the lung, such as bronchiectasis and empyema; infections of the genito-urinary tract such as prostatic abscess and urethritis; peripheral trauma and a relatively large number of infections of unknown origin. The course of the disease is usually foudroyant; half of the patients die within two weeks. Diffuse involvement of the cord and the fulminant course probably explain loss of tendon reflexes observed in at least half of the cases. In a few instances, the course may be marked by a period of invasion, followed by apparent resolu-

tion and then by gradual return of the symptoms. Evacuation of the abscess with subsequent recovery is almost a unique occurrence.

If an abscess interrupts the function of the spinal cord it is more commonly extradural than intradural in situation. Marked local pain, tenderness, symptoms and signs of sepsis and of compression of the cord usually occur.

The spinal cord may be involved in the course of a large number of the acute infectious diseases. Onset of paralysis is usually abrupt and the clinical picture is generally that of transverse myelitis. The story of poliomyelitis is too well known to bear repetition. Optic neuromyelitis occurs infrequently and derives its designation, as might be expected, from involvement of vision owing to optic neuritis and, subsequently, to rapid development of myelitis.

Tick Paralysis.—Tick paralysis, the cause of which is unknown, may affect man; the disease has a predilection for children. The disease is endemic in the sagebrush-bearing areas of western United States, British Columbia, South Africa and Australia. The patient who has this disease may retire at night in normal health and on attempting to get out of bed in the morning may fall to the floor. Usually, paralysis involves first the lower extremities, then progresses upward and can involve the thoracic musculature, muscles of deglutition and of phonation and may result in death. Paralysis may be associated with numbness of the hands and toes and there may be retention of urine or incontinence. The tick, probably the *Dermacentor venustus*, usually is found somewhere along the spinal column, particularly in the hair line. After removal of the tick by application of kerosene or by excision (care should be taken to remove its head), recovery usually takes place within a few days. The nature of the active agent and the exact site of its action are not understood.

Landry's Paralysis.—This is probably a clinical picture rather than a disease. Usually flaccid, rapidly ascending paralysis associated with loss of superficial and deep reflexes, sphincteric disorders and minimal disturbances of pain and sensation comprise its outstanding features. The paralysis may take a descending course and, occasionally, ocular palsy, headache, backache, and a slight degree of fever occur. There

are no constant changes in the cerebrospinal fluid. Acute toxic polyneuritis, progressive necrosis of the spinal cord and poliomyelitis may be some of the diseases that underlie Landry's paralysis.

CHEMICALS

Triorthocresyl Phosphate.—In 1930 there appeared an illness which was given appellations such as "jake leg paralysis" and "Jamaica ginger paralysis." The poisonous substance, triorthocresyl phosphate, probably introduced with denatured alcohol, was contained in an extract of Jamaica ginger that was ordinarily mixed with carbonated water and was used as a substitute for whiskey.

Individual susceptibility to this substance varied. Dull, aching pain in the calves of the legs often occurred from two to ten days after the extract had been imbibed. This was accompanied by progressive flaccid paralysis, particularly of the feet, legs and thighs, and frequently of the upper extremities; in some cases involvement of the medulla occurred. Numbness, if present, was usually transient and sensation was not altered greatly, but residual dysfunction of a disabling degree, resembling that of poliomyelitis, often occurred. Marked degenerative changes, sometimes accompanied by an exudate of lymphocytes, neutrophils, erythrocytes and fibrin, sometimes without evidence of inflammatory reaction, were noted in the peripheral nerves and in the cells of the anterior horns of the cord.

Apiol (Parsley-camphor).—This type of polyneuritis was not described prior to 1931. The earlier reports came from Holland, Yugoslavia, Germany and from other European countries where apiol was in use as an abortifacient. The cause of this neuritis was found to be not apiol, which, in itself, is not toxic, but triorthocresyl phosphate. Thus, apiol paralysis and Jamaica ginger paralysis had a common cause and ran similar courses.

Lead.—In lead neuritis, which need not be dealt with fully here, the situation of the lesion is difficult to determine. Prominent pathologic changes occur in the vessels, in the meninges and in the gray and white matter of the spinal cord. Such findings as the above and the occasional increase in cells of the spinal fluid, the diffuse, radicular distribution of the

lesion and limitation of the palsy to the motor field, suggest that part of the clinical picture of lead neuritis may depend on changes in the spinal cord.

DEFICIENCY

If subacute combined degeneration of the spinal cord associated with pernicious anemia can be regarded as owing to a deficiency of some sort, it expresses itself as a characteristic clinical picture. Paresthesia of the hands and feet such as suggests peripheral multiple neuritis is present in most cases. To what extent the paresthesia is dependent on degeneration of the peripheral nerves and to what extent it depends on changes in the spinal cord remain unknown. The cardinal findings occur in the realm of sensation. Impairment of all qualities of superficial sensibility, particularly over the lower extremities often can be demonstrated. More significant is marked impairment of deep sensibility, particularly of vibration in the lower extremities and in the lower portion of the trunk. Often associated with this there is impairment of postural sensibility and resulting ataxia. Tendon reflexes, especially those of the lower extremities, may be increased, diminished or absent. Babinski's sign and other pathologic plantar reflexes are often present and attest to involvement of the corticospinal pathways as well. If this dominates the picture, spasticity rather than ataxia occurs but both may be in evidence. If the disease is in an advanced stage, involvement of the sphincters occurs. Psychiatric disturbances of lesser or of greater degree are not rare.

It appears that this familiar picture can be brought about by chronic alcoholism, gastric carcinoma, obstruction, and by fistulas of the intestinal tract; by pernicious anemia, so-called prepernicious anemia and possibly by scurvy. It may be related similarly to pancreatitis and pellagra. The association of subacute combined degeneration of the spinal cord with these diseases may indicate some cause common to all, namely, the absence of Castle's factor. Degeneration of the spinal cord, which perhaps may be classified better as combined sclerosis, has been associated with various conditions, such as endocrine disorders, infectious and nutritional diseases, diseases caused by poisons, and other miscellaneous diseases. A picture suggestive of either subacute combined degeneration of the cord

or of multiple sclerosis is occasionally associated with the syndrome of postural hypotension.

DEGENERATIVE LESIONS

For want of better information some conditions may be listed tentatively as degenerative. In cases of senility, neurologic signs may be missing although there may be observed in the cord an increase in neuroglia, atrophy of nerve roots and of fibers in the periphery of the spinal cord without evidence of inflammation and independent of sclerosis of the vessels. Diminution of sensibility to vibration commonly occurs among patients beyond the fifth decade of life. It appears to be more commonly associated with hypotension than with hypertension and may occur more commonly among patients whose family histories give little evidence of longevity. Properly restricted, arteriosclerotic myelopathy is infrequent. Vibratory sensibility over the iliac crests and malleoli may be absent, the tendon reflexes may be absent and the sphincters may be paralyzed.

Amyotrophic Lateral Sclerosis.—This is a devastating fatal illness of subacute or of chronic course that usually affects patients of middle age and is characterized by a coexisting and usually symmetrical degeneration of the lower and upper motor neurons. Fibrillary tremors and atrophy of the somatic musculature, tongue and pharynx are commonly observed. The upper extremities usually become wasted and the lower extremities become spastic. When atrophy becomes extreme, loss of muscle leads to abolition of the otherwise hyperactive tendon reflexes. Pathologic plantar responses usually appear. As a rule, sensation remains unimpaired and the sphincters continue to function.

Primary Lateral Sclerosis.—This disease, which may be of familial origin, is a rare form of degeneration of the corticospinal pathways. Often the early clinical picture of some other disease that, as yet, has not made enough headway to be recognized, may simulate primary lateral sclerosis. This is likely to be true of multiple sclerosis. In the latter illness the common association of visual disturbances (indicative of retrobulbar neuritis or of palsy of extra-ocular muscles), nystagmus, tremor on movement, impairment of vibratory sensibility; absence of abdominal reflexes, signs of involvement of the pyr-

amidal tract, emotional lability; and the relatively frequent occurrence of precipitation of colloidal gold (in zone 1 of Lange's test) are of help in distinguishing between the two conditions. The sole findings in primary lateral sclerosis are those indicative of involvement of the pyramidal tract. Sensation is not impaired, the sphincters are not involved, and the disease usually progresses extremely slowly. In cases of Friedreich's ataxia, which frequently affects siblings, onset of the illness generally occurs in childhood; a striking degree of ataxia, pes cavus, scoliosis and cerebellar symptoms occurs.

Vascular.—Apoplexy of the spinal cord is rare but may be suggested by sudden onset of a transverse lesion of the cord among persons who are the victims of some other disease in which rupture of vessels may occur. Thrombosis of the anterior spinal artery also occurs uncommonly; its presence is suggested by rapid development of a transverse lesion of the cord, in which case appreciation of vibratory and postural sensibilities remains preserved. Rupture of vessels located extradurally but within the spinal canal, or thrombosis on the venous side also produces effects that may be transmitted to the cord. Too rapid decompression of patients who have caisson disease (diver's paralysis) may result in interference with the circulation through liberation of the nitrogen accumulated in the blood while under increased atmospheric pressure. It is particularly serious if the brain or spinal cord is involved.

DEVELOPMENTAL

Perhaps the commonest example of a disorder of this type is involvement of the spinal cord that may occur in the presence of spina bifida. This may be cystic or occult. The commonest site is in the lower portion of the lumbar and upper portion of the sacral region and the most common neurologic symptoms include paralysis, usually of a lower motor neuron type, incontinence, deformity of the feet and anesthesia variable in distribution. Usually there is associated a bony defect that can be demonstrated roentgenologically. Other findings that suggest the possibility of occult spina bifida are local hypertrichosis and pigmentation of the skin, a sacral dimple, deformity of the feet and spindly calves. Occasionally signs of involvement of the cord may progress or may appear later in

life. It is thought that these result from traction, from compression by a ligamentous strand or, rarely, from an associated tumor. Trophic ulcers, if they appear, usually do so after the fifteenth year of life. Surgical treatment may arrest unfavorable progress of these disabilities.

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THE RECOGNITION OF EARLY CARDIAC INSUFFICIENCY

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As a rule, late or severe cardiac failure, especially when associated with congestion, is not difficult to recognize. Early cardiac insufficiency, however, often is not recognized and in some instances it is difficult to distinguish the signs and symptoms of beginning failure from those owing to other causes. The cardinal signs and symptoms of cardiac failure are dyspnea, cyanosis and edema. In making a diagnosis of heart disease evidence is obtained from several sources; namely, the history, the physical findings and laboratory examinations.

In heart disease, as in many other diseases, the history often will give more important evidence than it is possible to get from other sources. It is rare to find evidence of a diseased heart in physical or laboratory examinations when some evidence of it could not be obtained from a carefully taken history.

It is common that a slightly diseased heart does not give any evidence of impairment of cardiac function. The history certainly is the most important source of information in detecting cardiac insufficiency, either early or late.

DEFINITION OF TERMS

By "early cardiac insufficiency" I mean the beginning of inability of the heart to carry on its functions. "Cardiac function"¹ means the ability of the heart to discharge its contents adequately and when the heart fails to accomplish this, the condition is manifested by dyspnea, cyanosis and edema, or by what is known as "congestive failure."

Dyspnea, difficult breathing, or breathlessness is one of the most, if not the most, important symptom in cardiology. Certainly it is the most important symptom in the recognition of early cardiac insufficiency.

The term "dyspnea" is often used loosely and often includes many types and degrees of difficult breathing. True dyspnea, or difficult breathing, almost always is more rapid than is normal respiration, but in some instances of dyspnea respiration is slower than normal.

SYMPTOMS AND SIGNS

Dyspnea and Exercise.—It is perfectly normal for healthy individuals to be dyspneic if they exercise sufficiently. Therefore, one should be careful to distinguish the normal from the abnormal. Tolerance to exercise will vary considerably with different individuals and will vary considerably with the same individual, depending on several factors, such as, obesity, habit and general physical condition. One of the early and very important signs of cardiac insufficiency is the actual beginning of true dyspnea and this will be manifested by the patient noticing that he becomes dyspneic, or more dyspneic than he has been previously, on doing some customary work or exercise. As the patient's cardiac insufficiency progresses, he will notice that his dyspnea gradually increases. That is, the patient will notice the same degree of dyspnea with less work and less exercise as time goes on. The development and progression of this dyspnea may be gradual and the dyspnea may be so mild that it may exist for months before the patient gives it much attention. The dyspnea may progress irregularly; that is, it may develop rapidly for a short time and then remain relatively stationary for some time. Lewis has called attention to the fact that true dyspnea should be graded not by the degree of distress the patient experiences but by the amount of physical effort that produces the dyspnea.

There is a definite correlation between the amount of the exercise and the degree of dyspnea, both in healthy individuals and in patients whose hearts are diseased. The common exercise that everyone participates in is walking and the degree of distress that this produces depends on several factors, such as speed with which one walks, whether the route is level or uphill, whether the walk is taken after a meal or when the stomach is empty, whether the air is still or whether it is necessary to walk against a cold wind. After a large meal, walking rapidly up a steep hill, on a cold day, against a strong

wind, and at the same time talking, will produce dyspnea in most healthy individuals.

In the early stages of cardiac insufficiency the patient will notice that he becomes slightly dyspneic on walking rapidly uphill. As his cardiac reserve decreases he will notice that he becomes dyspneic with less effort; that is, that he becomes dyspneic on walking a certain distance at an ordinary gait on the level, and as cardiac insufficiency increases he will notice that his dyspnea will be produced by walking shorter distances, and the condition may progress so that the patient will be dyspneic even at rest. At this late stage, there has been a general failure of the patient's circulation, congestive failure has developed and the patient's condition is evident to everyone. In this paper I am not interested in the stage of congestive failure.

The most important evidence of beginning failure, as has been said, will be obtained from the history. The patient will state that a certain act of exercise or work that he is accustomed to doing produces dyspnea, whereas previously, under identical circumstances, it did not. The most common indication of cardiac insufficiency is the history of diminished tolerance to exercise or of decrease in the patient's activities.

It is true that elderly people cannot engage in the strenuous work or exercise that they could engage in when they were younger. Several factors help to distinguish the decreased activities attributable to age alone from those attributable to cardiac insufficiency. Among elderly people the onset will not be so definite and the dyspnea will not be so prominent, nor will it progress as it will among those patients who have cardiac involvement. There also will be other signs and symptoms of age. Dyspnea owing to cardiac disease in most instances will have a definite date of onset and, as a rule, the dyspnea will definitely progress, even though it may be slight in some instances. When it becomes possible for the examiner to observe the dyspnea, or labored respiration, the cardiac disease will have developed far beyond the initial stage.

Several tests have been devised to measure cardiac efficiency. The measurement is made in terms of cardiac rate and blood pressure during exercise and at a certain time after exercise. These tests are not nearly as reliable, however, as

the history of dyspnea in giving information concerning early cardiac insufficiency.

Pain or Distress.—In a certain percentage of cases the first symptom of cardiac disease is slight pain or distress in the substernal area and over the epigastrium. At first, this pain is an uncomfortable feeling and may be slight. The significant features are that it comes only with exercise and is relieved by rest. The situation of the pain is significant. It is either in the substernal area or in the epigastrium, or both. Rarely, if ever, is the pain distributed over the precordium only. If the pain does occur over the precordium, the patient also will have pain in the substernal area or over the epigastrium. Often this distress, or sensation, noted by the patient will be merely a discomfort and will be brought on by walking after a heavy meal or against a cold wind. In this group of cases the pain will be experienced before the patient notices any interference with his respiration. The patient will learn early that he can obtain relief by retarding or stopping his activities and consequently he will stop exercising before he produces dyspnea. It will not be long after the onset of his pain that he will notice that there is some impairment of what he calls his "wind" or that his wind is not as good as it previously was and that he will puff or pant on doing certain exercises.

Palpitation.—Palpitation of the heart is a common complaint and often it is owing to beginning cardiac disease. Sometimes it has no clinical significance but whenever it is present an examination is indicated to prove whether or not it is the result of cardiac involvement.

Gastro-intestinal Symptoms.—Occasionally patients with beginning cardiac involvement will have symptoms referable to the gastro-intestinal tract. In some instances it may be difficult, in the early stages, to determine whether the disease is of cardiac or gastro-intestinal origin, or both.^{2,3} When one considers the pathologic changes that take place in the abdomen when the heart begins to fail, it is not difficult to understand why patients complain of symptoms that are referable to the gastro-intestinal tract. There is an engorgement of the capillaries, from both the arterial and the venous sides. This results in distention of the blood spaces and capillaries of the

abdominal organs, since these channels are capable of retaining a considerable portion of the total blood of the body. The structures in the abdomen that become affected by this early congestion are the liver, spleen and mucosa of the stomach and small intestine. Because of the congestion the function of these organs is disturbed. The patients will complain of gas and distress in the epigastrium. The important fact to remember is that these symptoms will appear only when the patients exercise and that they will get relief with rest. Patients who have symptoms referable to the gastro-intestinal tract have a cardiac difficulty that is further advanced than that of those patients whose first symptoms are slight dyspnea on accustomed exertion.

Cutaneous Signs.—Cyanosis, pallor and ashen gray tints are important factors in study of a patient. Their presence, when owing to cardiac disease, is usually evidence of a fairly advanced condition but, as a rule, they are not of particular value in diagnosing early cardiac insufficiency. It is true that some healthy individuals give a slight suggestion of cyanosis of the lips and nail beds. Cyanosis occurs most frequently and is most pronounced in the presence of valvular and congenital cardiac lesions. As a rule, when cyanosis is definitely present and is owing to cardiac insufficiency, one does not encounter much difficulty in establishing the diagnosis.

Edema.—Accumulation of serous fluid in the subcutaneous spaces, when it is owing to cardiac failure, usually represents fairly advanced cardiac disease and one does not have much difficulty in making the diagnosis. Occasionally one will see slight edema of the ankles of elderly individuals, evidently owing to slight cardiac insufficiency, but the patient will appear generally healthy and there will be few or no other signs of cardiac insufficiency. Occasionally a troublesome cough is a symptom of early cardiac insufficiency, owing to beginning congestion or edema of the mucous membrane of the trachea or of the lungs. When this is present there is usually other evidence of beginning congestion and the diagnosis is not difficult to establish.

CAUSES OF DYSPNEA THAT MUST BE CONSIDERED IN DIFFERENTIAL DIAGNOSIS

There are types of dyspnea that must be distinguished from that of beginning cardiac insufficiency. The more important of these are: (1) functional or nervous dyspnea, (2) dyspnea of a normal person, owing to increased exercise, (3) dyspnea of the effort syndrome, (4) dyspnea attributable to obesity, (5) dyspnea accompanying chronic bronchitis, (6) dyspnea of asthma, (7) dyspnea owing to emphysema, and (8) dyspnea attributable to bronchial or tracheal obstruction.

Nervous or functional dyspnea can easily be distinguished from dyspnea of early cardiac insufficiency in that functional dyspnea is characterized by a sighing type of respiration and is not associated with exercise; the patient often will complain that he cannot take a sufficiently deep breath. The dyspnea that occurs with exercise will not occur when exercise is of the normal or accustomed degree and it will not progress. The dyspnea that occurs with the effort syndrome is characterized by marked overaction of the heart but signs of organic heart disease are absent. The dyspnea owing to obesity is often difficult to distinguish from beginning cardiac dyspnea. It usually does not progress, organic heart disease is absent and the dyspnea improves or disappears with reduction in weight of the patient. Dyspnea owing to asthmatic bronchitis is variable and will increase and decrease with the severity of the asthma. It often occurs when the patient is at rest and it is accompanied by wheezing. Dyspnea of emphysema can be identified by the presence of the emphysematous thorax and by the absence of evidence of organic heart disease. In most instances it is not difficult to distinguish the dyspnea owing to beginning heart disease from that owing to other factors. The greatest difficulty arises when both conditions are present.

THE BENEFIT OF EARLY, ACCURATE DIAGNOSIS

It is just as important to recognize cardiac disease early in its course as it is to recognize any other disease when it is beginning. The information that will aid in establishing an early diagnosis will be subjective evidence, obtained from a painstaking history. The physician, in his zeal to make such a diagnosis as early as possible, may err on the side of com-

mission and by so doing he may make an invalid of a normal individual. If he is sufficiently painstaking in obtaining the history and interpreting it properly, however, he can avoid this danger in most instances. By recognizing cardiac insufficiency early, by giving the patient the proper advice and by instituting the proper treatment, it is possible to render to patients a greater service than can be conferred by waiting until the disease has progressed to a late stage.

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THE TREATMENT OF A FAILING HEART

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WHEN a heart burdened by the stress of disease can no longer adequately carry on the responsibilities of its function, it fails. Its failure may be abrupt, terminating in the sudden death of the patient or, more commonly, its failure may be gradual, resulting in the appearance of the well-known syndrome of congestive heart failure. This syndrome comprises dyspnea, often orthopnea, cyanosis, edema of the dependent portions of the body, accumulation of fluid in the serous cavities of the body, and chronic passive congestion of the viscera. Death may occur with the first bout of congestive failure but more commonly varying degrees of cardiac recovery occur and the patient survives one or more such episodes, with death ensuing at a more distant time.

Heart failure may be an eventuality in any form of heart disease. The various disturbances leading to heart failure, analyzed according to disturbances in the physiologic activity of the heart and circulation, are of utmost importance and interest, but regrettably are beyond the scope of this discussion. To state facts briefly, the heart is capable of responding, within certain limits, to an increased load by increasing its work. The limit of this response indicates the reserve of the heart. When disease impairs the ability of the heart to meet this added load imposed on it, failure in function inevitably supervenes.

The treatment of congestive heart failure is based, essentially, on three principles: 1. Therapeutic measures are directed primarily toward the heart to permit it to obtain more rest and thereby increase the efficiency of its function. 2. Therapeutic measures are applied principally to relieve sequelae of heart failure such as edema, accumulation of fluid in the serous cavities, anoxemia, increased venous pressure,

and so forth. Relief of these conditions obviates the burden of the heart. 3. Institution of an individualized regimen is directed toward the maintenance of an adequate circulation.

The first consideration in the treatment of congestive failure or impending failure is the placing of the patient at complete rest in bed in the semirecumbent posture. Physical rest should be as complete as possible and under usual conditions the patient must not be permitted to leave the bed. Granting bathroom privileges to these patients either completely defeats or to a great extent nullifies therapeutic efforts. Mental rest is likewise of great importance and during the first few days of failure, when the patient's sleep is disturbed by dyspnea or other discomforts contingent on his condition, the subcutaneous administration of morphine sulfate in carefully individualized doses frequently paves the way for improvement. When morphine is not well tolerated by the patient, the use of tincture of opium has proved to be of great value. Later, when greater improvement has occurred, the milder sedatives, such as the barbiturates, may be very satisfactorily employed, especially to promote restful sleep.

The diet of the patient with congestive heart failure is important and is based wholly on one premise, the reduction of the work of the heart, the same premise that motivates the application of other regulations. This may be accomplished by reducing the intake of food.

It is well known that the increase in basal metabolic rate, associated with hyperthyroidism and other conditions, and the increase in total metabolism, such as occurs in an obese person, may greatly augment the demands for work made on the heart. It has been clearly demonstrated that protein ingested in an amount that exceeds the replacement requirement of the body, is capable of accelerating metabolic processes, a phenomenon known as the specific dynamic action of protein. Thus, a meal rich in protein is capable of considerably increasing the work of the heart. On this basis, the reduction of protein in the diets of cardiac patients is indicated but caution must be used to avoid a ridiculously low intake of protein. Thus, under ordinary circumstances, the daily intake of protein would be reduced to 50 or 60 gm.

The energy of contracting muscle is chiefly derived from

carbohydrates. It is well known that glycogen is a necessary and important constituent of heart muscle and that its mobilization becomes extremely rapid in heart failure, particularly in the presence of anoxemia. The total daily caloric requirement can readily be furnished by a diet in which carbohydrate is predominant and the diet still will be palatable to the majority of patients.

Provision for a proper intake of vitamins and minerals must not be neglected and this can readily be accomplished by simple supplements.

Care must be exercised to prevent bulkiness of the diet. The necessity for limitation of the quantity of food is obvious. Restriction of the intake of fluids is of extreme importance and the degree of restriction must be determined by the circumstances in the individual case. The usual range of intake of fluids permitted within twenty-four hours is 900 to 1,500 c.c. It is well to restrict the use of table salt (sodium chloride), which diminishes thirst and permits the patient to submit to restriction of fluid with greater comfort.

Digitalis is the therapeutic agent most commonly used in heart failure and despite its availability to the medical profession for one hundred and fifty-three years, it is still one of the most misused drugs in present-day practice. The most striking indication for its administration is congestive heart failure, when auricular fibrillation is present, when the ventricular rate is rapid, and when a discrepancy exists between the apical and the peripheral arterial pulse rate. I do not wish to imply that these circumstances constitute the only indication for administration of digitalis but before discussing this problem further it becomes desirable to consider briefly the known actions of the drug on the diseased heart of man.

Notwithstanding the many actions that have been attributed to digitalis over the years, the proved effects now can be confined largely to three considerations: (1) Digitalis depresses the function of the sino-auricular and auriculo-ventricular nodes, resulting in a tendency to lower the cardiac rate. This is partly a vagal action, both central and peripheral. (2) It depresses cardiac conduction throughout the muscle and increases the refractory period of both the auricles and the ventricles. Depression of conduction, particularly conduc-

tion through the auriculoventricular (His) bundle, occurs. This explains the dramatic action of the drug in many cases of auricular fibrillation. (3) Digitalis increases the amplitude of cardiac contraction; it tends, also, to restore muscular tonus, apparently because digitalis acts directly on heart muscle.

With these actions of digitalis clearly in mind it becomes evident that its administration must rest on scientific principles rather than on faith. The physician stands in danger of prescribing digitalis on faith alone, for it has been administered for all forms of heart disease, regardless of the type of lesion that exists, or the state of function of the heart, and frequently on the mere suspicion of heart disease. Needless to say, such practice is to be condemned as not only being unscientific, but unnecessary and at times hazardous.

Although digitalis is indicated in many cases of heart disease, its most outstanding indication has been mentioned above; nevertheless its beneficial effects under other circumstances are prone to be less conspicuous. Such is the case of the patient with congestive heart failure whose heart beats in regular rhythm and not excessively rapidly. Additional therapeutic measures usually are necessary to restore more nearly normal cardiac function.

Whenever possible, digitalis should be administered orally. Under unusual circumstances, such as when nausea and vomiting are present as a result of visceral passive congestion, it may be given in a diluted form by rectum. Certain available preparations can be given effectively by deep intramuscular injection, the pharmacologic effect appearing within three to three and a half hours when relatively large doses are given.

Owing to the fact that some modern digitalis products do not conform to the potency established by the United States Pharmacopeia, it becomes desirable to prescribe the dose in the accepted unit of potency, the cat unit, rather than in terms of grains, grams, cubic centimeters and so forth, which may represent a considerable variation in potency. For example, a certain tablet of digitalis may contain 1 grain (0.065 gm.) of the drug equivalent in potency to one cat unit while another tablet containing $1\frac{1}{2}$ grain (0.1 gm.) of the drug represents the same potency.

In the average case of congestive heart failure wherein

digitalis is indicated it is well to begin administration of the product in doses of one cat unit three times daily after meals. It is given until nine or twelve cat units have been administered and in rare instances more than that; then administration of the drug is discontinued for four or five days, when it is resumed in the same dosage for two or three consecutive days each week. Some physicians prefer the continuous daily administration of smaller doses whereas my experience leads me to favor the intermittent method of dosage.

For oral use, several forms of digitalis are suitable provided that the product is fresh, of known potency, and of good quality. The powdered leaf of digitalis in capsules is a very satisfactory preparation as are likewise certain tablets and good tinctures. The infusion of digitalis is now rarely used, largely owing to its instability and variable potency. I wish here to condemn the use of pills or tablets containing absurdly small amounts of digitalis combined with various other agents of questionable value, in quantities that are pharmacologically ineffectual. When additional drugs are deemed necessary, let them be given separately and in adequate dosage.

Large individual doses of digitalis, orally or parenterally, are not to be recommended as routine procedures since in certain cases they may prove to be unnecessarily hazardous. When the indication for administration of digitalis is unquestionable and the necessity for prompt action is clear, five to eight cat units of a suitable sterile solution may be injected deeply into muscle.

The toxic effects of digitalis should always be avoided. Usually they consist of anorexia, nausea, vomiting and diarrhea. Severe intoxication, as evidenced by coupled beats, heart block and ventricular tachycardia are obvious dangers. Intoxication of the central nervous system by digitalis is a serious condition and one that apparently is not generally recognized. It frequently occurs without the more common toxic phenomena mentioned above and consists of drowsiness, disorientation regarding time and place, disturbed color vision (objects appearing yellow or green), frequently muttering delirium, and death. It is most likely to occur among older patients; therefore, digitalis must be very conservatively applied in treatment of elderly patients.

In partial or complete heart block, digitalis is usually clearly contraindicated. Its use in hyperthyroidism must be cautious. It is not usually indicated in coronary disease and frequently its use is hazardous.

Digitalis, when indicated and when adequately administered, aids materially in fulfilling the first principle in the treatment of heart failure, namely, to permit the heart to obtain more rest. This is largely effected by the slowing of cardiac rate and the consequently more effectual contraction.

The mercurial diuretics, salyrgan (mersalyl) and novasurol (merbaphen), have been the most outstanding contributions of recent years to the treatment of congestive heart failure. These preparations appear to act by mobilizing sodium chloride and water in the tissues and causing them to be excreted in the urine. The action presumably is exerted on the kidneys and the tissues of the body. Diuresis usually begins within a few hours after intravenous injection of 1 to 2 c.c. and the maximal effect of the single dose is invariably achieved within the first twenty-four hours. Injections may be given at intervals of two, three or four days. It is not unusual for the urinary output to range from 3,000 to 8,000 c.c. in the first twenty-four hours succeeding administration of the drug. Dramatic improvement in the patient's condition frequently occurs very soon after the release of large quantities of fluid, thus greatly relieving the load on the heart by lessening the peripheral resistance. The general circulation improves, venous stagnation disappears, venous pressure falls if the disease has caused it to be increased, and oxygenation of the tissues becomes more adequate.

The mercurial diuretics are contraindicated in the presence of acute glomerulonephritis but caution must be employed not to confuse evidence of heart failure reflected in the urinary tract, namely chronic passive renal congestion, with that of nephritis. Albumin, casts, and, at times, erythrocytes may be present in the urinary sediment when heart failure is marked. Enteritis is likewise a contraindication to the use of these mercurial products, which, at times, results in diarrhea. Extreme caution must be exercised in injection of these drugs, for introduction of minute amounts into the skin produces local necrosis of tissue following which considerable time is required for healing.

Long continued intravenous injection of the drugs named in the preceding paragraph may lead ultimately to local venous thrombosis and consequently their administration by this method becomes prohibitive. Under such circumstances they may be injected deeply into the muscles of the buttocks. This method of administration usually is attended by a slower action of the drug and less dramatic results. More recently, suppositories containing the mercurial products have been available but in my experience have not yielded results comparable with those obtained when the drugs are injected.

The diuretic salts, ammonium or potassium nitrate and ammonium or potassium chloride, are valuable adjuncts in the treatment of cardiac edema. At times the release of edema fluid by administration of the mercurial diuretics is slow and incomplete and supplemental use of the salts results in satisfactory diuresis. At times the use of these salts alone results in mobilization of fluid. They apparently act directly on the tissues of the body. An increased urinary output of water, acid, chlorides, ammonium salts, and total inorganic base occurs. The drugs are best given in enteric-coated pellets, and the usual dose is 4 to 6 gm. daily. Administration of the salts must not be too protracted, owing to the tendency of the concentration of urea in the blood of some patients to become elevated under their influence. It is frequently desirable to administer these salts three or four days preceding injection of the mercurial diuretics, and then to discontinue administration of the former. The presence of marked retention of nitrogen ordinarily would contraindicate use of the salts, but if other methods of treatment failed to mobilize retained fluids, their cautious use would be warranted. When the stomach will not retain medicines, as it will not at times when visceral congestion is marked or digitalis has been used unwisely, the salts may be administered in solution by rectum.

The purine diuretics likewise have a place in combating cardiac edema although they are usually less effective than the agents already discussed. They consist chiefly of theobromine sodium salicylate, theobromine, theophylline, theosine, and caffeine. They tend to cause liberation of water, sodium, and chlorides from the tissues and also apparently exert an influence on the kidneys. Their effect is largely on the peripheral

vascular system. These drugs usually are administered orally in doses of 0.3 to 0.6 gm., three or more times daily. When results are not evident within a few days, their continued administration is of doubtful value.

The slow intravenous administration of sterile hypertonic solution of glucose frequently is an important adjunct in the treatment of heart failure. It has already been emphasized that glycogen is a very important constituent of heart muscle and that it is rapidly mobilized and lost during heart failure. Its replenishment to some degree is possible by the intravenous administration of glucose. This may be given in concentrations of 15 to 20 per cent in quantities of 400 to 500 c.c., or concentrations up to 50 per cent may be given in smaller amounts. This procedure may be repeated daily for several days.

From time to time a patient with congestive heart failure is encountered who is literally water-logged, yet who at the same time presents all evidences of dehydration. The retained fluids are not available for use by the organism; they are bound in the various tissues of the body. Likewise, under such circumstances, intravenous administration of hypertonic solution of glucose may prove to be a lifesaving expedient.

Venesection, one of the oldest therapeutic procedures, occupies an important place in the treatment of congestive heart failure. It is particularly effective when venous pressure is increased, for it reduces the volume of venous blood, which diminishes the pressure of the blood in the heart in diastole, thereby diminishing cardiac dilatation and making possible more efficient cardiac contraction. This procedure often permits the heart to keep pace with, or even to overcome, the load, and frequently this is the turning point in the restoration of more efficient cardiac function. The quantity of blood withdrawn usually ranges from 300 to 600 c.c., and the procedure may be repeated from time to time as indications arise.

Administration of oxygen is at times valuable but should not be used as a routine procedure. It is only of value when an atmosphere of increased oxygen content can be utilized. In many instances of congestive failure the function of the lungs has become so impaired that oxygen cannot be absorbed and obviously under such circumstances this method of treatment

is futile. Oxygen is best administered by use of the portable tent.

Other mechanical measures employed in the treatment of congestive heart failure consist of aspiration of retained fluid from the body cavities, introduction of Southey's tubes into edematous extremities, or multiple puncture or cutaneous incision of the edematous parts. Fortunately, however, these procedures rarely have been necessary since the advent of the mercurial and other diuretics.

Thus, the second principle in the treatment of heart failure is met: treatment directed against the sequelae of heart failure.

The final problem when cardiac function has been restored is the development of a properly individualized regimen in an attempt to maintain competency of the heart and to defer the inevitable recurrent failure. This comprises physical restrictions, frequent periods of rest, the adoption of a new philosophy of life, recurrent treatment, careful observation, and frequent examination. These measures obviously must be individualized, depending on the type of heart disease present, the degree of impairment and many other factors too numerous to mention.

The ideal cardiac regimen is not complete unless it includes well planned recreation. In advising the patient to obtain more rest and relaxation, perhaps changing his occupation or requiring him to retire from active life, the fact is often overlooked that even though the body is placed at relative rest, the mind remains active and that some minds require considerable attention. If this important phase of the management is neglected many patients become morbid, discouraged and very unhappy. The physician must be a psychotherapist and must meet these problems in each case. Occupational therapy, scientifically directed, does much to help the patients spend their time happily and usefully. Likewise, sedentary hobbies should be encouraged.

Exercise as a measure in the maintenance of good general health is beneficial in heart disease, provided that the cardiac reserve is sufficient to permit it safely. Walking is probably the best form of exercise because it can be controlled. These measures must be carried out under close supervision so that the patient at all times remains well within his threshold of cardiac tolerance and therefore within his threshold of safety.

THE CLINICAL SIGNIFICANCE OF LEAD IV OF THE ELECTROCARDIOGRAM

ARLIE R. BARNES AND DON J. WOLFRAM

THE steps in the research that led Wolferth and Wood to advocate and initiate the use of lead IV in the study of acute myocardial infarction in animals and in man represent a logical and brilliant development in electrocardiography. Some other observers who reported their experience with the fourth lead seem to have been carried away by their enthusiasm. They professed to see in the fourth lead a superiority over the standard leads so great that one gained the impression that they were almost willing to dispense with the standard leads as far as recognition of acute myocardial infarction was concerned. In 1934, one of us¹ challenged this preoccupation with the fourth lead and emphasized the importance of familiarity with the changes in the standard leads which are indicative of myocardial infarction. This failure to recognize, or at least to acknowledge, changes in the standard leads and the tendency to claim that diagnostic changes were present only in the fourth lead, when actually the standard leads likewise were diagnostic, has been pointed out by Roth in a discriminating article. The conclusion of that analysis was that the extraordinary claims for superiority of the fourth lead arose from failure to recognize and to grasp the significance of changes occurring in the standard leads. Roth felt that the articles bespoke "a wish for an open sesame into the hidden realms and manifold sequestered channels that lead to a diagnosis in cases of myocardial disease." In the light of further experience it is desirable to attempt an evaluation of the clinical worth of lead IV of the electrocardiogram. The knowledge on the subject is not all in and the final word cannot be said. Much needs to be said to avoid undue enthusiasm on the one

hand and, on the other hand, to point out significant values of the fourth lead in conditions other than acute myocardial infarction.

It is unfortunate for the discussion of the normal variations of the fourth lead of the electrocardiogram that a variety of applications of the electrodes have been employed by various investigators. While certain generalizations are possible relative to all the methods, yet sufficient variations from the normal occur in the various applications of the electrodes to warrant separate discussion for each. Until now three applications of the electrodes have been used chiefly. The right arm electrode (exploring electrode) may be applied over the apex and the left arm electrode (indifferent electrode) may be applied on or near the vertebral column, on a level with the anterior electrode. This will be designated the "apex-vertebral lead" in the present discussion. The application may be varied in that the left leg terminal may be utilized as the indifferent electrode. This will be designated the "apex-left leg lead." A third application consists in placing the right arm terminal (exploring electrode) anteriorly, to the left of the sternum in the fourth interspace. The posterior or indifferent electrode is applied as described in the first method. This will be designated the "left pectoral-vertebral lead."*

A number of valuable studies of the normal fourth lead have been made and are summarized in the tabulation.

The characteristics of the normal fourth lead, as indicated by these studies^{3, 5, 6, 11, 14} may be summarized as follows: While inversion of the P wave is the rule, the wave may be upright, diphasic, or iso-electric. Absence of the Q wave is always abnormal, a Q wave of less than 1 mm. is probably abnormal

* The chest leads employed in this laboratory and reported here were obtained by a modified left pectoral-vertebral application of the electrodes. The right arm electrode is applied anteriorly in the fourth interspace slightly to the left of the left border of the sternum. The left arm terminal has the left vertebral application. With these galvanometer connections relative positivity of the precordial electrode is represented in the finished curve by a downward deflection and relative negativity of this electrode by an upward deflection. Despite its inaccuracy the first downward deflection of the initial ventricular complex will be designated a "Q wave" and the following upward deflection an "R wave" in deference to the current practice. Subsequent tracings will be taken to conform to the recommendations of the Committee on Standardization of the Fourth Lead.

TABULATION
STUDIES OF THE NORMAL FOURTH LEAD

	P wave.	Q wave.	QRS complex.	RS-T segment.	T wave.
Shipley and Hallahan, 21 cases*	90 % inverted 10 % diphasic or iso-electric	Always inverted	Always simple QR type; slurring and notching common		Always inverted
200 cases†	25 % upright 45 % inverted 29 % diphasic 1 % iso-electric	Always present Minimum 1.4 mm. Maximum 3.3 mm. Average 9.7 mm.	85% QR diphasic. M complex, slurring, and notching common. Occasionally monophasic	Usually depressed. Maximum elevation 0.6 mm. Maximum depression 2 mm.	Always inverted
Sorsky and Wood, 114 cases‡	20.1% upright 42.9% inverted 29.8% iso-electric 7.0% biphasic	Inverted. Minimum depth, 2.0 mm.	Biphasic. M and W complexes and notching common	Usually iso-electric. Maximum depression 2 mm. Rarely elevated	Always inverted
114 cases‡	17.5% upright 48.3% inverted 21.0% iso-electric 13.1% biphasic	Inverted. Minimum depth, 1 mm.	Biphasic. Slurring and notching common	Usually iso-electric. Maximum depression 2 mm. No elevation	96% inverted 4% upright
Katz and Kissin, 25 cases§	Usually inverted	Varied from 1 to 19 mm. Average 8.5 mm.	Diphasic. Never monophasic	Usually iso-electric. Occasionally depressed to 2 mm. Never elevated	Usually inverted. Maximum depression 8 mm. Diphasic once
Master, 104 cases§	Inverted	Always inverted. 1.5 to 14 mm. Average depth 5.3 mm.	Always diphasic. Never notched or slurred. R waves 2.5 to 17 mm. high	Usually 1 mm. below iso-electric line. Occasionally iso-electric. Never elevated	Always inverted. 1 to 6 mm.

* Indicates apex-ventral lead. † Indicates apex-left leg lead. ‡ Indicates left pectoral-ventral lead. § Indicates left pectoral-ventral lead.

and if it is less than 1.4 mm. should be regarded with suspicion. Notching or slurring of the QRS complex or QRS complexes of "M" or "W" configuration occurs in normal tracings. The R-T segment usually is iso-electric but normal elevations of 0.5 mm. may occur. Depressions of the R-T segment up to 2 mm. may occur in normal tracings. The T wave is always inverted in the apex-left leg lead but rarely may be diphasic or slightly upright in the left pectoral-left leg lead. T waves greater than 9 mm. are not uncommon in normal tracings. Upright T waves are frequently encountered in examination of normal children.^{7,8} If the left leg terminal is substituted for the vertebral electrode in the apex-vertebral lead, occasionally a small initial upward deflection before the usual deep downward excursion may appear. Substitution of the left sternal application of the anterior electrode for the apex position in the apex-left leg lead occasionally results in biphasic or slightly upward T waves.

The fourth lead has been advocated as chiefly useful in the study of myocardial infarction. As will be emphasized, it has a much wider field of usefulness in the study of a variety of cardiac diseases. Intelligent use of the fourth lead is impossible without familiarity with, and simultaneous evaluation of, the changes occurring in the standard leads. So far as recognition of acute or healing acute myocardial infarction goes, there is some doubt whether there is such a thing as a "specific" or "pathognomonic" pattern of changes in the fourth lead.

The fourth lead has its greatest usefulness in identifying acute myocardial infarction involving the anterior and apical portion of the left ventricle. The changes which are most characteristic in the early phase of acute infarction are disappearance of the Q wave or a Q wave less than 1 mm. in amplitude, depression of the S-T segment more than 2 mm. and the development of a diphasic or upright T wave. These changes may appear very shortly after onset of the attack. The deviation of the S-T segment may appear earlier and be greater in magnitude than the deviations of the RS-T segments in the standard leads (Fig. 112). Absence of the Q wave may persist for many years as the most reliable, or only, relic of anterior infarction when the other changes in the fourth and standard leads have approached, or have returned to, normal (Fig. 113,

d). This absence of Q_4 persists even though the patient has a second infarction involving the posterior and basal portion of the left ventricle. The complete absence of Q_4 must always be construed as a sign of previous acute infarction of the anterior portion of the left ventricle, unless some other condition, such as hypertension or pericarditis, can be held accountable for the change.

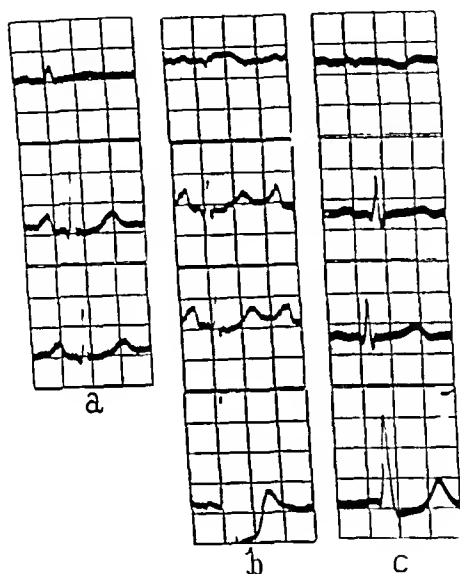


Fig. 112.—Patient 1. Tracing made in an attack of coronary thrombosis: *a*, standard leads one day after attack. *b*, Standard leads and precordial lead two days after occlusion. In lead IV note absence of Q wave, marked depression of the S-T segment and the upright T wave. Significant changes in the standards leads are: low voltage QRS in lead I, dome shaped and elevated S-T segment in lead I, slight depression of S-T segment in lead III. *c*, RS-T segment deviations disappearing in standard and fourth leads. Patients are numbered in these legends so that the reader may know which tracings apply to the same patient and which to different patients. In all illustrations leads are represented, from above downward, in the following order: I, II, III, IV.

The deviation of the S-T segment in lead IV persists, on the average, much longer than does RS-T deviation in lead I, which usually has returned to normal limits in one to four weeks. The T wave in lead IV may remain positive for months or years but in general it tends to revert to normal. The T wave may return to normal in as short a time as three to four weeks, although usually much longer than that is required

(Fig. 113, *a, b, c, d*). In an occasional instance, in the presence of a classical history of infarction, the T wave may become positive while the Q wave remains normal (Fig. 114). In two such cases there was a history of more than one infarction and the standard leads indicated that infarction of both the anterior and posterior portions of the left ventricle had taken place successively.

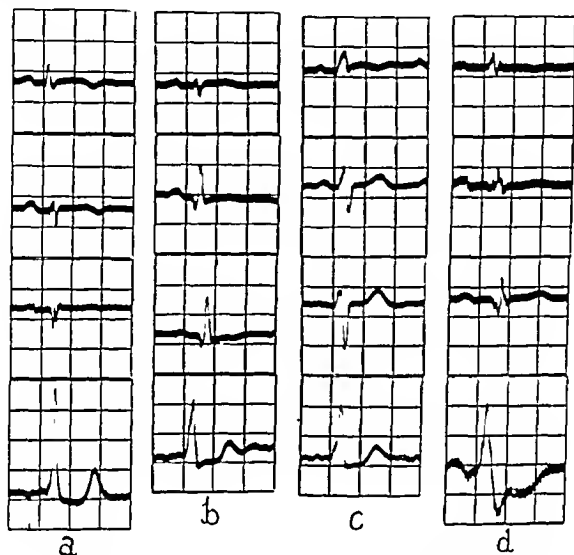


Fig. 113.—*a*, Patient 2. Tracing taken four weeks after infarction of anterior apical portion of left ventricle. T_4 upright. S- T_4 slightly depressed. *b*, Patient 3. Two months after coronary occlusion. Standard lead relic of infarction includes low voltage QRS in lead I; dome shaped S-T segment, lead I, and shallow inversion of T_1 . Q_4 is absent, T_4 is upright and S- T_4 is depressed. *c*, Patient 4. Four and a half months after infarction. The absent Q_4 , the depressed S-T segment, and the upright T wave in lead IV confirm the residuum of infarction present in the standard leads. *d*, Patient 5. Tracing taken six years after acute myocardial infarction. The absent Q_4 , the shallow negative T_1 with a preceding S- T_1 of iso-electric level are relics of previous acute anterior infarction.

In acute anterior infarction the changes in the fourth lead may be more clear-cut than the changes in the standard leads at certain stages after acute infarction. This is particularly true when the amplitude of lead I is low, preventing recognition of deviation of the R-T segment or inversion of the T wave in that lead (Fig. 113, *b, c, d*). In the vast majority of

cases, careful study of the standard leads in serial tracings reveals evidence of acute anterior infarction of value equal to those observed in the fourth lead. In a great many cases reported in the literature, wherein it was held that the fourth lead alone was diagnostic, it turns out that there was a failure to recognize and accredit the changes in the standard leads, as Roth pointed out. In occasional instances of undoubted acute infarction the diagnosis is corroborated by changes in the

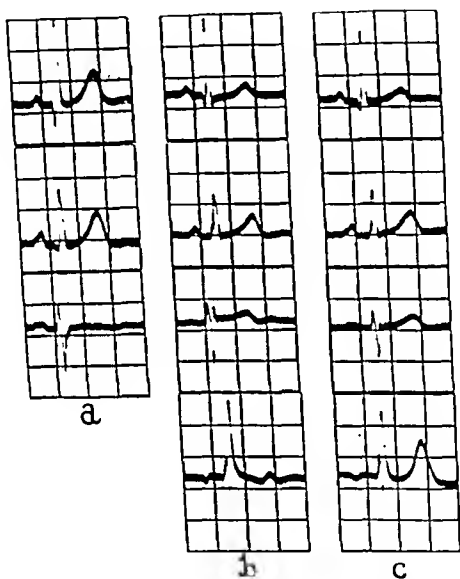


Fig. 114.—Patient 6. Typical attack of acute coronary thrombosis, December 8, 1937. No clinical evidence of pericarditis. *a*, Electrocardiogram taken one day before acute attack. *b*, December 13, 1937. T_4 upright and Q_4 diphasic (?). Voltage of T_1 and T_2 decreased and of T_3 increased. *c*, December 29, 1937. Exaggerated positive T_4 .

fourth lead in the absence of any diagnostic changes in the standard leads (Fig. 114). On the other hand, in three cases that we have observed, with excellent histories of acute coronary closure, the standard leads gave clear-cut evidence of anterior infarction when the fourth leads approached or had returned to normal (Fig. 115). It is important to note that the presence of bundle-branch block profoundly modifies the fourth lead, leading to frequent absence of the Q wave and abnormal deviations of the R-T segment. It is important to

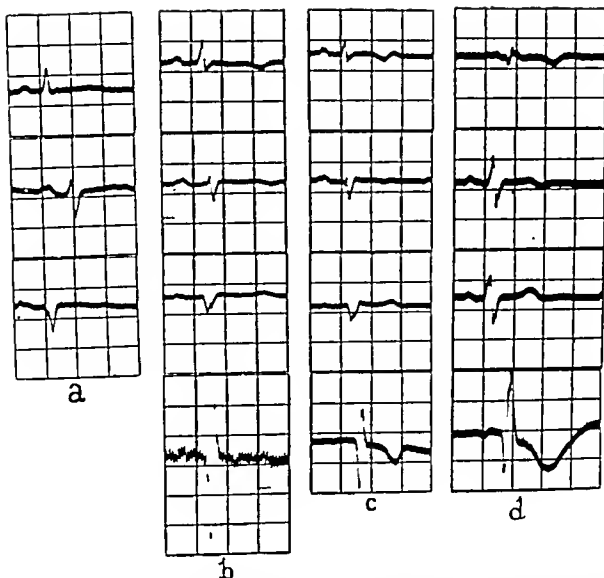


Fig. 115.—Patient 7. *a*, Electrocardiogram taken two days before infarction, showing low voltage T waves in the standard leads. *b*, Three days after coronary occlusion. T_1 and T_2 inverted without deviation of S-T segments. T_4 iso-electric (?). *c*, Twelve days after occlusion. Shows relic of anterior infarction in the standard leads with a normal fourth lead. *d*, Patient 8. Standard leads contain relic of anterior infarction while the fourth lead is essentially normal.

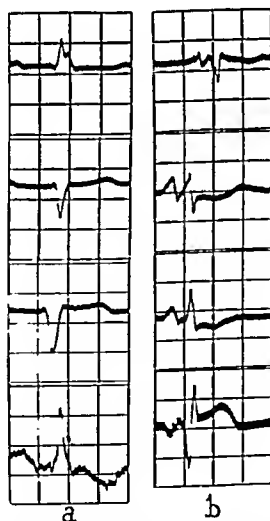


Fig. 116.—*a*, Patient 9. No history of angina pectoris or coronary occlusion. Tracing shows partial bundle-branch block. Note the abnormally small Q_4 . In other cases of bundle-branch block (*b*, patient 10) T_4 may be upright and R- T_4 elevated. Extreme caution must be observed in drawing inferences from lead IV in the presence of bundle-branch block.

avoid drawing conclusions about acute infarction from changes in the fourth lead in the presence of bundle-branch block (Fig. 116).

In recognition of acute infarction of the posterior basal portion of the left ventricle, the changes in the Q_3T_3 pattern in the standard leads are infinitely superior to any abnormalities of the fourth lead. Wolferth and Wood have called atten-

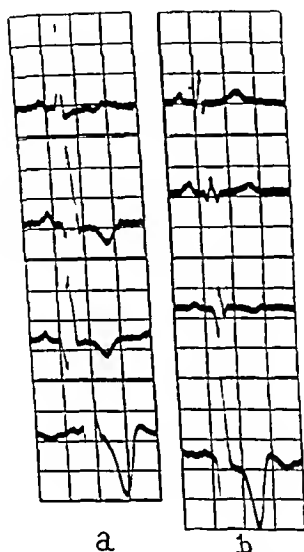


Fig. 117.—*a*, Patient 11. Patient had long-standing hypertension. Coronary occlusion occurred three weeks previous to time tracing was taken. The negative T_1 in association with the depressed $S-T_1$ are accounted for by the hypertension. The cove plane T_2 and T_3 waves are indicative of posterior infarction. The deep Q_4 and T_4 and tall R waves are rather frequently seen in posterior infarction. *b*, Patient 12. Coronary occlusion eight weeks previously. The Q_3 pattern and negative T_3 in the standard leads are relics of posterior infarction. The exaggerated Q , R and T waves in the fourth lead are of some value in corroborating the other evidence of posterior infarction.

tion to that. After the first few hours following acute posterior infarction, the fourth lead may be normal. In the first few hours the $R-T$ segment may be slightly or definitely elevated and this may be followed occasionally by a shallow, iso-electric or small upright T wave but this is of brief duration. The Q_4 is commonly within normal limits. We have been struck by the tendency of the Q , R , and T waves to have large amplitude

in the presence of Q_3T_3 types of patterns with standard leads, although this has not been uniformly true (Fig. 117, *a*). This cannot be relied on in view of the great range of amplitude shown to be within the normal variation for normal subjects but may have corroborative value (Fig. 117, *b*). It can be stated definitely that the Q_3T_3 pattern of posterior infarction

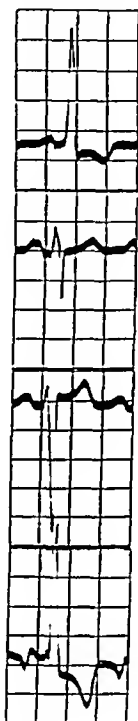


Fig. 118.—Patient 13. The patient had severe hypertension. As evidence of left ventricular strain in the standard leads, note the marked left ventricular preponderance and the negative T_1 associated with a depressed $S-T_1$. Note the absent Q_4 and the depressed $S-T_4$ despite the absence of any clinical evidence of myocardial infarction.

is exceedingly more common and of much longer duration than any changes seen in the fourth lead.

Whether or not abnormalities of the fourth lead can be correlated with coronary sclerosis in the absence of coronary occlusion remains to be determined. The question will be answered only by studies at necropsy which establish the diagnosis of coronary sclerosis and exclude previous coronary occlu-

sion and a variety of other conditions known to cause changes in the fourth lead. Caution about premature conclusions on this question, based on uncritical studies, is strongly to be urged.

The fourth lead in cases of chronic left ventricular strain undergoes a variety of changes in the absence of any evidence of angina pectoris or coronary thrombosis. Not infrequently the Q wave is diminished (1 mm. or less) and in a certain pro-

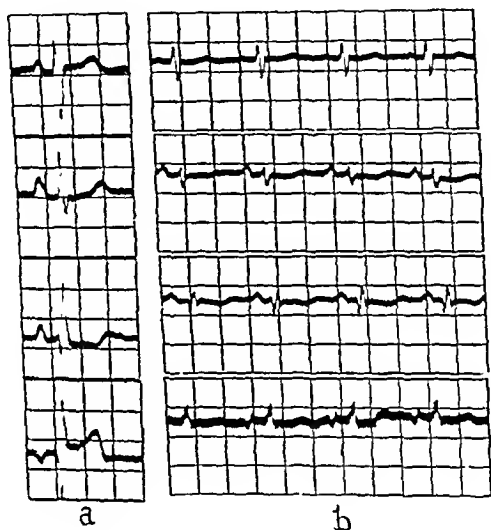


Fig. 119.—*a*, Patient 14. Electrocardiogram of a patient with chronic right ventricular strain. Characteristic features in the standard leads are: right ventricular preponderance, prominent S_1 and Q_3 , diphasic T_3 with T_1 and T_2 upright. In lead IV, note the elevation of the R-T segment and the upright T wave. *b*, Patient 15. Another instance of chronic right ventricular strain. Changes in the standard leads include negative T_3 and diphasic T_2 . In lead IV, observe the absence of the Q wave, the depressed S-T segment, and the upright T wave. This could easily be confused with anterior infarction if the clue to the proper diagnosis was not sought in the standard leads.

portion of cases the Q wave is absent.² The S-T segment may be depressed below the normal limit of 2 mm. The T wave usually is negative but may be shallow or diphasic (Fig. 118). In one case T_4 was upright but there was a possibility that coronary thrombosis had occurred. In a considerable percentage of cases of uncomplicated hypertension or aortic valvular disease, all the components of the fourth lead are within nor-

mal limits. Standard leads showing left axis deviation, a negative or diphasic T wave in lead I with the S-T segment arising below the iso-electric line, will serve to identify the changes in the fourth lead with chronic left ventricular strain rather than with coronary occlusion.

Chronic right ventricular strain associated with emphysema, disease of the pulmonary artery, pulmonary stenosis, and patent ductus arteriosus may produce important changes in the fourth lead. The Q_4 deflection may be exaggerated, normal, diminished (1 mm. or less) or may be entirely absent (Fig. 119, *b*). The T wave in lead IV may be normal but frequently it is diphasic or upright. Definite elevation of the R-T segment may occur and in no instance have we seen depression greater than the normal variation (Fig. 119, *a, b*). Here again consideration of the pattern in the standard leads reveals a picture which serves to relate the changes in the fourth lead to chronic right ventricular strain. The changes in the standard leads include right axis deviation, upright, diphasic, or inverted T_2 , inversion of T_3 and not rarely a prolonged Q wave in lead III. In the most marked case the R-T segment in lead I may be slightly elevated while the S-T segment in lead III is slightly depressed (Fig. 119, *a*).

In acute pulmonary embolism, changes similar to those occurring in chronic right ventricular strain may be observed in the standard and fourth leads. The Q wave in lead IV usually is within normal limits, although occasionally it is diminished (1 mm. or less). T_4 may be diphasic or iso-electric but usually is upright. The R-T take-off is iso-electric as a rule but occasionally a very slight elevation occurs. The standard leads exhibit a prominent S_1 , an upright or diphasic T_2 with a tendency for S- T_2 to take off below the iso-electric line, a negative T_3 with an R-T contour of the cove plane variety occasionally, and a prominent Q_3 . The T_3 may be diphasic or iso-electric in less typical cases (Fig. 120, *a, b*).

In acute septic pericarditis the Q_4 may be preserved, although occasionally, it is greatly diminished or absent. Experimental evidence indicates that rapid intrapericardial effusion sufficient to produce cardiac tamponade elevates R- T_4 above the iso-electric line. We have not had the opportunity of observing that condition clinically. So far as our experience

goes at present, we have not observed deviations of R-T₄ greater than the normal in uncomplicated cases of septic pericarditis. T₄ may be normal but often it becomes shallow, iso-electric or sharply positive. Again the RS-T phenomena in the standard leads furnish the clue to the meaning of changes observed in the fourth lead. Elevation of the R-T segment in leads I and II, and occasionally in all leads, is

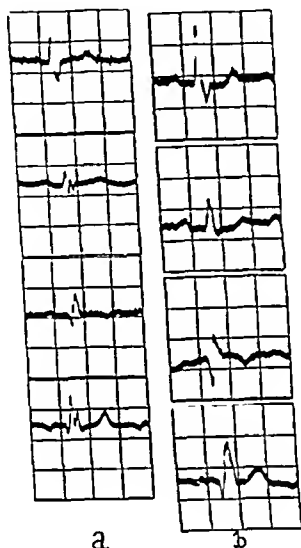


Fig. 120.—*a*, Patient 16. Electrocardiogram taken shortly after lodgment of a pulmonary embolism (acute right ventricular strain). Observe the right ventricular preponderance, the prominent S₁ and Q₃, the inverted T₃ with the R-T₃ segment iso-electric. Lead IV shows a diminished Q wave and an upright T wave. *b*, Patient 17. Pulmonary embolism. The cove plane R-T₃ segment and inverted T₃ resemble the changes observed in posterior infarction; however, the right ventricular preponderance, the prominent S₁ and Q₃, the upright T₂ (usually negative in posterior infarction), and the upright T₄ (usually undisturbed in posterior infarction) give the clue to the correct diagnosis.

frequently observed. In the leads in which elevated R-T segments occur the segments end either in an exaggerated T wave or have a broadly rounded, dome shape. Either succeeding these R-T level changes or at times without their occurrence, the T waves may be inverted chiefly in leads I and II but at times in all leads and the R-T segment preceding the negative T waves may have the normal take-off and cove plane

appearance seen in late stages of myocardial infarction. The tendency of the changes is to revert rapidly to normal as recovery from the pericarditis occurs (Fig. 121).

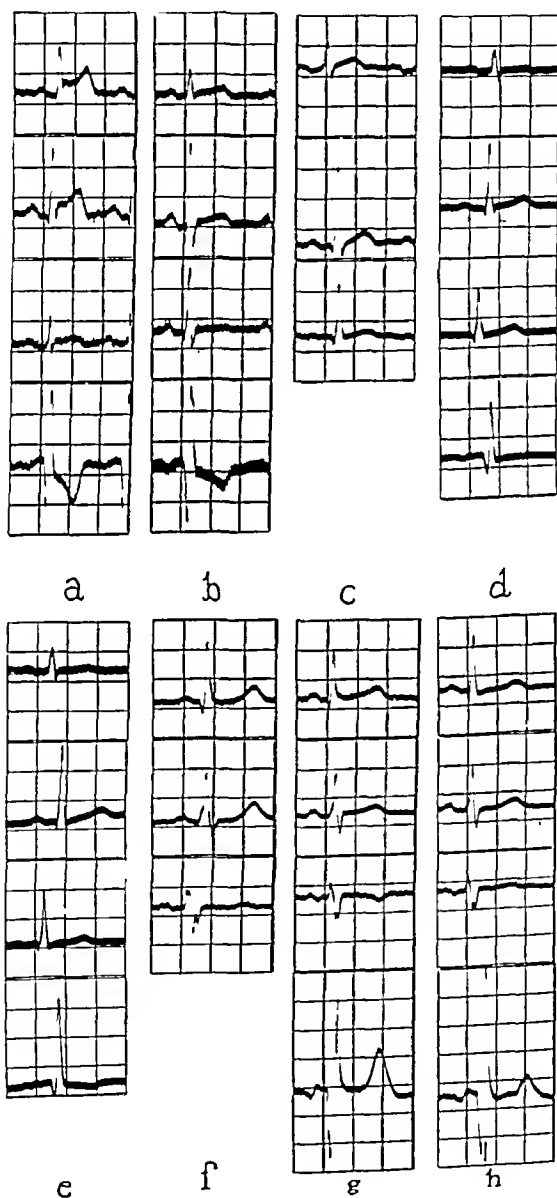


Fig. 121.

In chronic constrictive pericarditis the Q_4 usually is normal. Occasionally it is diminished or absent. No cases showing significant deviation of $R-T_4$ have been observed. In more than half the cases T_4 is positive. The standard leads may exhibit two types of changes suggesting that the electro-

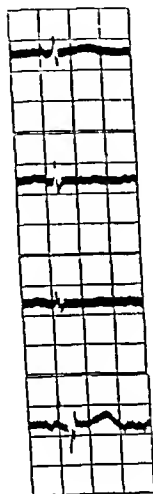


Fig. 122.—Patient 21. Electrocardiogram of a patient with chronic constrictive pericarditis. Note the low voltage of the QRS complexes and T waves in the standard leads and the upright T wave in lead IV.

cardiographic changes are owing to chronic pericarditis. These are low voltage in all the leads and inversion of the T waves in all leads. Failure of shift of the electrical axis in electrocardiograms taken with the patient in various positions is some-

Fig. 121.—*a*, Patient 18. Electrocardiogram five days after onset of acute pericarditis. Note elevated R-T segment in all leads but chiefly in leads I and II. The fourth lead is essentially normal. *b*, Same patient three days later. *c*, Patient 19. Electrocardiogram on admission of patient with clinical symptoms and physical findings of pericarditis. *d*, Same patient two days later. Note rapid disappearance of elevation of RS-T segments in the standard leads. T_4 iso-electric. *e*, Same patient two days after *d*. Standard and fourth leads rapidly returning toward normal. *f*, Patient 20. Preoperative tracing. No cardiac symptoms. *g*, Same patient; electrocardiogram taken six days after onset of epigastric and substernal pain with physical findings of pericarditis. No T or Q pattern of acute myocardial infarction in the standard leads. T_4 positive and exaggerated. *h*, Same patient nine days after *g*. Electrocardiogram beginning to return to normal.

times observed and is confirmatory evidence of chronic adherent pericarditis (Fig. 122).

Deviation of the R-T segment in lead IV has been observed as a result of treatment with digitalis¹² and in association with marked and sudden increase in intrapericardial pressure. Rheumatic carditis has been shown to change the size or direction of T₄ in some cases.⁴

Thus, a great variety of clinical cardiac conditions other than coronary occlusion can produce changes in the fourth lead. These changes include diminution or absence of the Q wave, significant deviations of the R-T segment and reversal of the normal direction of the T wave. It is obvious that there is no change in the fourth lead alone that can be considered diagnostic of acute myocardial infarction.

To interpret the clinical significance of changes in the fourth lead it is necessary to consider at the same time the character of the changes in the conventional leads. To make such an interpretation presupposes thorough familiarity with the clinical significance of the various patterns of changes observed in the standard leads. Used in that way the fourth lead will complement, amplify and extend the meaning of the changes in the standard leads. Sometimes the changes in the standard lead will be more diagnostic than those in the fourth lead. At other times, the reverse will be true. Again they will be equally diagnostic and frequently only by considering the standard and fourth leads in conjunction can useful clinical inferences be drawn. Intensive study of the standard leads must not be neglected if it is desired to derive the fullest value from the fourth lead and to avoid pitfalls in its interpretation.

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SOME NOTES ON THE DIAGNOSIS OF CONDITIONS ASSOCIATED WITH ASCITES

ALBERT M. SNELL

RICHARD CABOT began the chapter on ascites in his book on differential diagnosis with the simple statement, "I recently made a series of wrong diagnoses in cases of ascites" and he notes, further, that his errors were shared by some of the best diagnosticians in this country. Few clinicians of experience have not been involved in similar errors; the difficulty appears to be owing to the fact that the types of cases in which mistakes most often are made at first glance appear to be perfectly simple and obvious examples of familiar disorders.

For some years it has been the practice at the Clinic to refer patients who have ascites, the cause of which was not apparent immediately, to the gastro-intestinal service for study. The experiences to be reported here largely derive from this practice and the patients in question all had one thing in common; they were suspected of having some type of hepatic disease. In other words, the group in question was a selected one, the diagnostic field having been narrowed considerably by exclusion of patients who had ascites owing to obvious carcinomatosis, to obvious cardiac disease, or to renal disease. The diagnostic study of such patients is simplified by having knowledge of the statistical frequency of the causes of ascites, by understanding the physiologic mechanisms involved and by a systematic gathering of clinical and laboratory evidence.

STATISTICAL CONSIDERATIONS

Cabot's figures on the relative frequency of the causes of ascites are of great interest. In his series of 224 necropsies, the four common causes of the condition were cardiac weakness, neoplastic peritonitis, renal disease and cirrhosis of the

liver, in that order of frequency. These causes, taken together, accounted for the ascites in 88 per cent of cases in the group. His examination of the clinical records of the Massachusetts General Hospital from 1870 to 1910 revealed 3,047 examples of ascites and in that series the distribution differed considerably, neoplastic peritonitis dropping in frequency and the first four causes of ascites being cardiac weakness, renal disease, hepatic cirrhosis and peritoneal tuberculosis in that order of frequency. In that series these four etiologic factors explained, at least to the satisfaction of the clinician, the presence of ascites in 86 per cent of the whole group. At the Clinic we do not encounter the large group of patients who have decompensated rheumatic heart disease that one observes in most large teaching hospitals, although the so-called surgical types of abdominal disease are encountered here in abnormally high frequency. For our purposes then we are in the habit of considering in the differential diagnosis of ascites the following common causes: (1) cardiac incompetence; (2) chronic glomerulonephritis, or nephrosis; (3) various types of parenchymatous liver lesions of both specific and of nonspecific origin; (4) peritoneal tuberculosis; (5) peritoneal carcinoma; (6) various types of pelvic tumors, and (7) polyserositis. The order of frequency here is only an approximate one but is sufficiently accurate to be useful.

PHYSIOLOGIC MECHANISMS

To facilitate proper understanding of the diagnostic problem it is necessary to have in mind some of the known physiologic mechanisms which may be involved in production of ascites. Among these may be mentioned: (1) increased venous pressure, which is most frequently caused by congestive heart failure or by an adherent pericardium, but which may be local in its distribution as is the case when portal stasis is present; (2) reduced osmotic pressure of the blood serum, dependent on a low concentration of serum albumin, a condition encountered in its purest form when so-called lipoid nephrosis is present but which, as will be shown, also obtains when parenchymatous disease of the liver is present; (3) combinations of the two factors just mentioned, a situation that exists when cirrhosis is present; in such cases, portal venous hypertension

and reductions in the values for plasma proteins combine to produce transudation of fluid, and (4) irritation of the peritoneal surfaces, such as that produced by inflammatory changes or by neoplasm.

CLINICAL AND LABORATORY INFORMATION NECESSARY FOR DIAGNOSIS

The differential diagnosis of ascites has been discussed so fully in works on physical diagnosis that complete presentation of the subject will not be attempted here. Rather, the information necessary for diagnosis in the doubtful case will be considered.

Many of the serious errors made in diagnosis of ascites could be eliminated if making snap judgments were avoided scrupulously. While in some cases diagnosis is ridiculously easy, systematic approach to each case as an individual problem is the safest course. Differential diagnosis, as a rule, is based almost entirely on objective evidence but, not infrequently, there are features in the history which deserve attention. Any account of dyspepsia or of abdominal pain should be analyzed carefully for a possible clue as to the presence of an abdominal neoplasm. In one case recently encountered at the Clinic an alert house officer made the diagnosis by obtaining a history of dysphagia and postprandial distress, which led to detection of a high-lying gastric carcinoma with peritoneal carcinomatosis. A history of tuberculosis is of importance for obvious reasons. If a previous history of jaundice is presented one must inquire into the possibilities of the presence of idiosyncrasies to drugs, with especial reference to antirheumatic remedies; possible earlier exposure to arsenic and to alcohol also must be investigated. If diarrhea is mentioned, the possibilities of the presence of pancreatic disease with secondary fatty change in the liver, or of hepatic metastasis from pancreatic carcinoma come into consideration. An inquiry also should be made into the matter of gastro-intestinal bleeding; this is important for it may call attention to the presence of esophageal varices, or of bleeding neoplastic lesions in the gastro-intestinal tract.

Among the important points in physical examination, the

presence or absence of adenopathy deserves consideration; enlarged supraclavicular and umbilical lymph nodes are commonly found in the presence of abdominal malignancy and, if present, serve to establish the diagnosis. Physical examination of the heart and lungs ordinarily will reveal any of the more obvious lesions of these organs which might explain collection of fluid in the abdomen. The abdomen then should be examined with the patient in the vertical and also in the horizontal position. If fluid is free within the peritoneal cavity, the abdomen will assume a flattened, or batrachian contour when the patient is supine, whereas when malignancy involves the peritoneum or when tuberculous peritonitis is present the abdomen tends to maintain its globular shape regardless of the patient's position. Demonstration of masses within the abdomen may be very difficult if the abdomen is tightly distended by ascites. *Ballottement may be employed to advantage in determining the size of the liver and spleen but in general it is best to tap the abdomen before any conclusions are drawn as to the presence of an abdominal or of a pelvic tumor.* The relative sizes of the liver and spleen are of obvious importance because splenomegaly is observed rarely in association with malignant lesions and occurs commonly in association with primary hepatic disease. Digital examination of the rectum of every patient and careful pelvic examination of all women is of the utmost importance; presence of a rectal shelf or of perirectal infiltration suggests the presence of neoplastic peritonitis, while demonstration of a pelvic mass or of uterine fixation calls attention to the possible presence of tumors, of ovarian cysts, or of pelvic tuberculosis. If cirrhosis or if other conditions associated with the presence of free fluid in the peritoneal cavity are present, the pelvic viscera are ordinarily found to be flattened out low in the pelvis.

The presence of hernia is also of diagnostic importance. In one series of 112 patients who had portal cirrhosis we⁵ found that a total of forty-nine of these had hernia and, in some of these individuals, hernia preceded development of ascites. Collateral circulation is also a significant finding in hepatic disease. While the classical caput medusae is not often seen, there may be other large dilated veins present over the abdomen and over the thorax which indicate that portal ob-

struction exists. Esophageal varices give evidence of the presence of internal collateral circulation; they may be demonstrated readily by roentgenologic examination or, in exceptional instances, esophagoscopy may be justified.

Laboratory examinations will assist in the diagnosis in many instances. In addition to routine urinalysis, the serologic test for syphilis and roentgenologic examination of the thorax, it is advisable to make a careful examination of the stained blood smears. In the majority of cases of primary hepatic disease there is a definite macrocytic anemia which is almost diagnostic in itself; in occasional instances, the presence of leukemia also may be demonstrated in this manner. In the presence of any syphilitic lesion of the liver of sufficient magnitude to produce ascites, strongly positive findings on serologic tests are almost the rule; a negative result from the Wassermann test, therefore, more or less excludes syphilitic hepatitis from consideration. Bromsulphalein tests of liver function are also of great value. Strongly positive results of the test are the rule in the presence of parenchymatous disease of the liver of any type, whether benign or malignant, whereas the absence of retention of dye is very strong evidence against the presence of a primary hepatic lesion sufficient to cause ascites. In such cases another cause must be sought for carefully. If jaundice is present involvement of the liver by whatever pathologic process is present may be assumed to have occurred.

Recently, we have been impressed by the fact that when hepatic disease is present a marked reduction of the total plasma proteins occurs, but, more particularly, the total serum albumin is reduced. The proteins ordinarily are not reduced as much when hepatic disease is present as when nephrosis is present, but the concentration of serum albumin may be at or below the edema level. It is not uncommon, however, to find patients who have ascites owing to hepatic disease, whose total plasma proteins are normal in amount; the only evidence of abnormality is reversal of the normal albumin-globulin ratio. Because the "salting out" methods by which this ratio is determined are admittedly imperfect, attempts have been made to estimate directly the colloidal osmotic pressure of the serum. Butt and Keys have shown in a selected group of proved cases of hepatic disease that reductions of osmotic pressure of more

than 40 per cent are the rule in these cases. It is probable that, in the future, direct measurement of the osmotic pressure will be used in place of the somewhat less reliable methods of study of plasma proteins and that such estimations will constitute an essential part of the study of any patient who has ascites.

Ascitic fluid should also be examined when obtained. Chylous, turbid, or bloody fluids are indicative of malignant involvement of the retroperitoneal nodes or of the peritoneal surfaces. The protein content of ascitic fluid is particularly significant; if it exceeds 1.5 per cent, the fluid probably is an exudate; the common causes of exudates are malignancy or tuberculous peritonitis. In the occasional case carcinomatous cells may be demonstrated in the stained smears; their presence, of course, is indicative of extensive peritoneal involvement. The so-called malignant cells are probably nothing more than irritation forms of normal endothelial structures. Little can be learned by bacteriologic study, although in some cases inoculation of guinea-pigs may be necessary.

If metastatic malignancy of the liver is suspected, hepatosplenography following injection of thorotrast (thorium dioxide solution) may be helpful. Cirrhotic lesions produce a finely granular, homogeneous shadow while metastatic conditions are revealed in the liver as large negative shadows which lie within the hepatic substance. This method of study has been criticized on the ground that thorotrast is a radio-active substance and that it may produce some harm to the patient. However, Yater and coworkers, whose extensive experience with this work entitles them to give an authoritative opinion, have encountered no difficulty from this source; furthermore, for many patients who have ascites, the prognosis of a long life is most uncertain. Therefore, it seems justifiable to administer thorotrast rather than to take the greater risk of performing laparotomy to establish a diagnosis. Finally, a trial of diuretics may give some useful information; when syphilitic hepatitis or cardiac disease or renal disease is present, good diuresis is usually obtained whereas when tuberculous peritonitis or neoplasms are present, little or no effect is expected. The patient who has cirrhosis may or may not have an increased output of urine after administration of mercurial diuretics. Diuretics should be used cautiously and febrile reactions, hematuria, or

inadequate diuretic response should be considered contraindications to their continued use.

SPECIAL DIAGNOSTIC POINTS

Pelvic Tumors.—Among the more puzzling diagnostic problems encountered among patients who have ascites are those presented by female patients who have pelvic tumors of various types. Detection of a very large ovarian cyst is often a most difficult matter and it is remarkable how frequently such patients may present themselves and state that a diagnosis of hepatic cirrhosis has been made previously. The two features which have been most helpful in making the diagnosis are the absence of retention of bromsulphalein and the persistently globular contour of the abdomen. When these two findings coexist the possibilities of the presence of a pelvic tumor are sufficiently great to warrant exploration when in doubt. Papillary cystadenomas usually are easily demonstrated on pelvic examination even without resorting to paracentesis. Solid tumors of the ovary are a considerably more difficult problem and are, in addition, relatively rare. Osler's description of two such cases is, of course, classical. One patient who was examined at the Clinic underwent repeated paracenteses and diuretics were employed extensively with fairly good effect. The clinical picture suggested the presence of cirrhosis but the absence of any definite evidence of hepatic disease led to performance of exploration and a solid, fibrous tumor of the ovary, about the size of a grapefruit, was found. This was situated high within the abdomen and it could not be detected by ordinary abdominal palpation. Its removal resulted in complete and permanent cure. The mechanism by which such tumors produce ascites is entirely unknown.

Tuberculous Peritonitis.—This is a sufficiently uncommon disease that the physician is not on the alert for it and it is the source, therefore, of many errors in diagnosis, as was demonstrated by the recent case of a man who gave a history of alcoholism; his physician had made a very unfavorable prognosis on the ground that the patient had portal cirrhosis. This patient had marked ascites and edema but no objective evidence of hepatic disease; the usual tests of hepatic function with bromsulphalein gave entirely negative results. This find-

ing led to performance of exploration at which time the presence of extensive tuberculous involvement of the peritoneum was demonstrated. The patient has fully recovered. It must also be recalled that tuberculous peritonitis is not uncommon as a terminal lesion of patients who have hepatic cirrhosis; its presence under such circumstances rarely is detected except at necropsy or in the course of exploration.

Syphilitic Hepatitis.—This is a condition which presents no difficulty in diagnosis in its earlier stages, at which time, usually, strongly positive results from serologic tests lead to the diagnosis. Frequently patients are encountered who have had the benefit of long continued antisyphilitic therapy, which is sometimes followed by reversal of the Wassermann reaction and by late development of ascites. Such patients frequently present the pathologic picture of atrophic cirrhosis and it is an extremely difficult matter to evaluate the relative effects of the original disease and the effects of the treatment which has been directed against that disease. Also, occasionally the original diagnosis of the patient's condition was debatable; whatever lesions exist in the liver may be owing to overzealous treatment which may contribute to development of arsenical hepatitis. Finally, the possibility of obtaining falsely positive results from serologic tests in the presence of hepatic disease has to be considered, as well as the fact that a patient may have both atrophic cirrhosis and latent syphilis which have no relationship to one another.

The Pick-Concato Syndrome.—This condition should cause little difficulty in diagnosis if its existence is borne in mind. Its extremely chronic nature and the eventual involvement of all serous surfaces are the distinguishing features by which it can be recognized. Calcification of the pleura or of the pericardium is a late development which may be recognized by roentgenologic examination. It is important to note that the "Zuckergussleber" characteristic of the disease, because of long-standing passive congestion, may give evidence of some functional damage, notably a reduction in the rate of elimination of bromsulphalein.

Cirrhose Cardiaque.—This is a term which has been applied to describe a patient who demonstrates the features of both cardiac incompetence and cirrhosis of the liver, the latter

being supposedly owing to long-standing passive congestion. The evidence of such changes in the liver has been both denied and affirmed and it is not uncommon to observe, on examination of some patients, that the effects of chronic passive congestion may simulate those of cirrhosis very closely. Boland has recently reviewed a series of cases of congestive heart failure in which necropsy was performed, with special reference to the changes produced in the liver. He found that actual destruction of the parenchyma of the liver and replacement fibrosis are rare occurrences. He suggested that a liver which has suffered from passive congestion may be more than ordinarily vulnerable to endogenous and exogenous toxins and that the occasional appearance of cirrhosis may be explained on this basis.

Rare Causes of Ascites.—Among the rare causes of ascites may be mentioned echinococcus disease, amebic hepatitis, parasitic disease (notably schistosomiasis); the various forms of leukemia with hepatic infiltration, visceral Hodgkin's disease and amyloidosis. Diagnosis of parasitic disorders obviously depends on demonstration of the presence of the parasite in question. Primary amyloid disease of the liver is diagnosed rarely during life. If the condition is associated, as is usually the case, with syphilis, with tuberculosis, or with chronic suppuration, diagnosis is easily made, but when the so-called idiopathic cases are encountered diagnosis of the condition is difficult, if not impossible, during life. Patients who have symmetrically enlarged livers and have marked albuminuria may be subjected to a Congo red test, employing the Paunz technic. This may be of diagnostic value.

In recent years three additional and rather unusual causes of ascites have come to light: (1) The first of these is the so-called essential thrombophilia⁶ associated with progressive and repeated thromboses which form in veins in various parts of the body. If the portal system is involved, as it may be in the later stages of the disease, ascites develops invariably. Diagnosis depends on obtaining a history of repeated venous occlusion and on demonstration of an abnormally rapid coagulation of the blood. (2) Fatty lesions associated with pancreatic atrophy or with stone⁸ also have been recognized recently as causes of ascites. They are of considerable im-

portance since the condition will respond to treatment with high lecithin diets, with choline and with lipocaic. The condition is probably more common than has been supposed and a series of cases from the Clinic have been described recently. (3) Finally, Binger and Keith have called attention to the presence of ascites and of edema of indeterminate origin in cases having the common factor of a marked hypoproteinemia with no demonstrable cardiac, hepatic, or renal disease. The underlying etiologic factors are not clear and the condition is presumably dependent on the presence of some inherent defect in protein metabolism.

It seems appropriate to conclude this discussion with some general comments in regard to diagnosis and treatment. Errors in diagnosis are best avoided by making a systematic approach to the subject and by analyzing all factors which might have a bearing on the doubtful case. While it is conceded that in most cases diagnosis is a relatively easy matter, snap judgments, especially those which attribute ascites to the presence of portal cirrhosis, are to be carefully avoided. Diuretics, particularly the mercurials, should be used with caution and their use may be deferred until the abdomen has been tapped and until ascitic fluid has been subjected to chemical and microscopic study. Repeated examination of the abdomen, pelvis and rectum after tapping, with the patient relaxed by means of a hot tub or by means of a sedative, is a simple and readily available method of avoiding serious error and should never be omitted. Use of the bromsulphalein test to determine hepatic function, and determination of either the serum protein or the osmotic pressure, will either eliminate hepatic disease from consideration or will make it a major possibility. If there are strong suspicions of neoplasm, hepatography with thorotrast is entirely justifiable in order to avoid useless or unnecessary medical and surgical procedures which can be of little help to the patient.

Peritoneoscopy has been a valuable diagnostic aid in skilled hands but, unfortunately, it has not been used widely. It is the opinion of many conservative surgeons in this country that it is better to examine the abdominal viscera through a small incision, obtaining if possible specimens for biopsy, than it is to depend on peritoneoscopic study. This practice has much

to recommend it and should be advised particularly when dealing with women in whose cases pelvic tumors cannot be absolutely excluded from consideration and among individuals of both sexes who are suspected of having tuberculous peritonitis.

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CHEMOTHERAPY OF INFECTIONS OF THE URINARY TRACT

EDWARD N. COOK AND WILLIAM F. BRASCH

From time to time new drugs are presented to the medical profession for use in treatment of disease. In the past few years two new preparations have been used extensively in treatment of infection of the urinary tract. They are mandelic acid and sulfanilamide. Although either one may be used, each drug has its own indications; we shall consider each drug separately.

Mandellic acid is an aromatic hydroxy acid which is known chemically as hydroxyphenyl acetic acid. For more than half a century it has been known that, if given orally to dogs, this drug is excreted in the urine in almost the same amount as that given.

Although the ketogenic diet is difficult to administer, the excellent results obtained when properly given suggested the advisability of applying a similar but simpler method of treatment. Betahydroxybutyric acid, which is the active bacterial agent of the ketogenic diet, when given by mouth is oxidized to carbon dioxide and water unless the patient is in a state of ketosis. In search of a similar acid, Rosenheim suggested the use of mandelic acid and he and other workers have demonstrated the definite bacteriostatic and bactericidal properties of this drug, both in vitro and in vivo, by its effect on bacilli that are usually the cause of infection of the urinary tract.

At present, the ammonium salt of this acid usually is used and is administered in the form of syrup or elixir. It is necessary to give the equivalent of 12 gm. of the pure acid daily; this is best divided and given in four doses, one after each meal and at bedtime. Because of the frequent gastrointestinal disturbances which accompany its absorption, we



we seen gross hematuria. In all cases, hematuria disappeared when administration of the drug was discontinued.

Sulfanilamide is the amide of sulfanilic acid, which is known chemically as p-amino-benzene-sulfonamide. It has been used extensively during the past year and already has proved to be an excellent therapeutic agent in many conditions. Urinary infection has responded very well to its administration and the drug has become a very useful addition to the armamentarium of the urologist.

The exact mode of action of sulfanilamide is not understood. Many observers have demonstrated that it is absorbed rapidly from the intestinal tract, that it is transported by the blood and is excreted in the urine. During the period of administration, concentrations slightly lower than those in the blood occur in the prostatic secretion, in pleural and peritoneal effusions and in the spinal fluid. Appreciating these facts, it seems reasonable to assume that the tissue fluids also maintain an appreciable concentration of this drug during administration.

In treatment of infections of the urinary tract, sulfanilamide is used in dosages varying from 40 grains (2.6 gm.) to 75 grains (5.0 gm.) daily. Our usual procedure is to start treatment with the larger dose for the first two or three days; then the dosage is reduced to 40 grains (2.6 gm.) and is continued at that level for six to eight days. Among elderly individuals, tolerance to the drug is definitely lower than among young individuals; therefore, we feel it is advisable to use a dosage of 40 grains (2.6 gm.) throughout the whole course of treatment of elderly subjects. In treatment of gonorrhea we usually start with 75 grains (5.0 gm.) daily and reduce the dosage gradually after two or three days to 60 grains (4.0 gm.), and then, after a similar period, to the maintenance dose of 40 grains (2.6 gm.). This is continued for a period of eight to twelve days.

As with mandelic acid, the bacilli that usually cause infection of the urinary tract respond very well to administration of sulfanilamide. Likewise, the uncomplicated cases respond more favorably than do conditions complicated by the presence of stone, tumor, or some other lesion. In treatment with sulfanilamide, maintenance of any particular pH is not absolutely necessary and, consequently, this drug is of the greatest value

believe it advisable to reduce the dosage during the first twenty-four hours. After that time the prescribed dosage usually is tolerated well. Administration of the drug is continued for eight to twelve days, depending on the case. If, at the end of this period, the urine is not sterile, we believe it advisable to discontinue medication for ten to fourteen days and then institute a second course of treatment. The main reason for this is that the organisms seem to acquire a tolerance to the drug after a certain length of time.

As a concentration of 0.5 per cent mandelic acid, or greater, and a pH of 5.5 or lower in the urine are necessary if a bactericidal urine is to be obtained, consideration of two points becomes essential to satisfactory management of patients undergoing this form of therapy. First, in order to maintain sufficient concentration of this drug in the urine, the intake of fluid must be limited to six or seven glasses of fluid daily. Second, a satisfactory pH of the urine must be maintained. Extensive use of the ammonium salt of mandelic acid has demonstrated that supplementary use of acidifying drugs is required less frequently than it was formerly. However, in about 10 per cent of cases the desired pH cannot be maintained without addition of ammonium nitrate, ammonium chloride, hydrochloric acid or nitrohydrochloric acid. In certain instances, use of an acid ash diet or even a ketogenic diet has been resorted to in order to obtain the desired results. There yet remains a relatively small group in which it is impossible, at the present time, to produce urinary acidity of sufficiently effective degree.

In treatment of uncomplicated bacilluria mandelic acid is efficacious in 90 per cent of cases. But, if such a condition is associated with prostatitis, cicatricial deformity, stone, tumor, or obstruction to flow of urine anywhere along the urinary tract, the percentage of good results declines rapidly. However, in such cases use of the drug is of value as a palliative measure or as a procedure preliminary to instrumentation or to operation on the urinary tract.

Mandelic acid must be given with care, particularly to patients who have reduced renal function. Nausea is, by far, the most common complication following its administration; tinnitus, headache, and diarrhea rarely occur. Occasionally, microscopic hematuria may be noted; only in three cases have

we seen gross hematuria. In all cases, hematuria disappeared when administration of the drug was discontinued.

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when treating infection of the urinary tract caused by organisms of the genus *Proteus*. Sulfanilamide is of particular value in treatment of a certain group of cases, namely bacteriuria associated with chronic prostatitis. Clear definition of this group is not possible yet, but apparently it is that group in which prostatitis is associated primarily with bacilluria.

In treatment of the group of coccal infections, sulfanilamide is not as effective as in treatment of the group of bacillary infections. There is one organism of this group, the *Streptococcus faecalis*, which rarely responds well to administration of mandelic acid.

There are many untoward reactions caused by absorption of sulfanilamide. Some are of a mild degree and do not require withdrawal of the drug. Headache, vertigo and nausea frequently are observed. Vomiting is not common. A mild degree of cyanosis must be watched closely and, if it becomes more severe, the drug should be withdrawn. It may herald the onset of sulphhemoglobinemia, agranulocytosis, or acute hemolytic anemia. Presence of any cutaneous eruption precludes use of the drug and its administration should be discontinued immediately.

Both mandelic acid and sulfanilamide should be given with circumspection and patients receiving such medication should be observed carefully. Mandelic acid is certainly less toxic than sulfanilamide and, for this reason, should be used in the larger percentage of cases. Sulfanilamide remains the drug of choice in treatment of infection caused by organisms of the genus *Proteus* or infection of the urinary tract associated with marked prostatitis.

fessed that the line of distinction is often difficult to draw. Often what seems to be acute prostatitis is really a small, superficial abscess of a prostatic duct, the presence of which is proved only by appearance at the urethral meatus of a small drop of pus owing to rupture of the abscess into the urethra. Fortunately, spontaneous rupture into the urethra is a very common means of termination of prostatic abscess.

Signs and symptoms of acute prostatitis vary according to the degree of severity of the attack. The mild attack elicits only complaints of a feeling as of weight in the perineum, frequency of urination, and delay or difficulty in starting the urinary stream. If the attack is severe or if it is complicated by the presence of abscess, local symptoms become pronounced and general symptoms are elicited. The pain in the perineal region may be very intense and there is usually a constant desire to urinate. Sitting down, crossing the legs, indeed, any movement may increase the pain; defecation may cause great distress. Occurrence of painful priapism usually adds to the patient's discomfort and urination becomes increasingly difficult. By this time, the patient usually appears very ill, the temperature ranges from 101° to 104° F. (38° to 40° C.) and often is accompanied by chills. There is usually an increase in the concentration of urea of the blood, especially if retention of urine occurs. Examination by palpation through the rectum at this time discloses that the prostate gland is enlarged as a whole or in part, that its consistency is not normal and that there is a feeling of tenseness of the gland. If an abscess has formed, a soft, fluctuant portion often can be felt. Examination causes great distress and only gentle palpation is tolerated.

Treatment.—This consists of rest in bed and application of hot packs to the perineal and suprapubic regions; the patient can be given hot sitz baths. All local treatment of the urethra, of course, must cease. Only moderate amounts of fluids should be given by mouth. Use of codeine sulfate and acetylsalicylic acid, or of opium and belladonna suppositories will make the patient fairly comfortable. A hot rectal douche consisting of physiologic saline solution (110° F., 43° C.) administered twice daily is advised if the patient can tolerate such treatment.

Complete retention of urine should excite suspicion that an abscess is developing; under such circumstances a soft rubber catheter should be used to empty the bladder. This always should be done with the aid of either local or general anesthesia. Determinations of the concentration of urea of the blood should be made and, if the concentration continues to increase, the prostate gland should be drained through either the urethra or the perineum.

CHRONIC PROSTATITIS

Chronic prostatitis may be a sequel of acute prostatitis or may be insidious in its onset. The most common symptom of chronic prostatitis is increased frequency of urination, and the act of urination usually is accompanied by some pain or burning. Chronic infection of the prostate gland may be entirely asymptomatic, or may produce one or all of five groups of symptoms; namely, the urinary, genital, sexual, general and focal groups.

Evidence of focal infection of the prostate gland may be found in other parts of the body owing to three factors, namely, localization of infection in other organs, action of toxins and reflex or referred symptoms. Lesions of the eye are presumably the result of infection. Arthritis is caused either by infection or by action of toxins. Complaints regarding the stomach and the back usually are of reflex origin. In 25 per cent of cases of chronic infection, the prostate gland was found to be normal on digital examination through the rectum. In 38 per cent of such cases, the urine was normal and, in a great many instances, there were no symptoms referable to the genito-urinary tract. Thus, when dealing with a condition that is suspected of being focal in origin, it is important to investigate the prostate gland, irrespective of local signs or symptoms.

Technic of Examination and Diagnosis.—Investigation of the prostate gland should include the following procedures: (1) palpation through the rectum to determine the size, consistency and sensitivity of the gland; (2) microscopic examination of the expressed secretion; (3) culture of the secretion.

To the examining finger the gland may feel enlarged or decreased in size, but the important factor is its consistency. If the prostate gland is the seat of chronic infection, usually it

is not elastic and uniform to the touch, but feels hard and has an irregular surface. Tenderness may be elicited as the finger passes over the entire gland or only over certain portions of it. To establish the diagnosis of prostatitis of clinical significance, the expressed secretion must contain pus cells. These cells are more granular and somewhat larger than are ordinary leukocytes. The presence of clumps of pus cells, which are formed by plugging of the prostatic ducts by secretion, is sufficient evidence to establish a diagnosis of chronic infection. The number of such clumps found bears a direct relationship to the degree of infection present. Other constituents of the secretion derived from an infected prostate gland are degenerated leukocytes and epithelial cells. By far the most important diagnostic procedure is that of culturing the prostatic secretion.

Until the past few years, most authorities agreed that 80 to 90 per cent of cases of chronic infection of the prostate gland were of gonococcal origin. Records of the Clinic for the past few years show that 56 per cent of all patients who had chronic prostatic infection gave no history of having had gonorrhea. The mode of infection in this group was through hematogenous or lymphogenous routes from some other focus of infection in the body; tonsils and teeth were, by far, the most common source of infection. Carbuncles, boils, influenza and severe bronchitis are also responsible for some cases of prostatic infection. Some of the clinical entities of proved prostatic origin are arthritis, spondylitis, calcaneal spurs, neuritis, sciatica, myalgia, fibrositis, ocular infections, secondary anemia, indeterminate lower abdominal pain, torticollis, and so forth. Inoculations of animals with material obtained from a group of these patients, cultures of material from which were positive, have shown interesting sites of localization and the lesions produced in the experimental laboratory were found typical of the lesions of these patients.

Treatment.—Bacteriologically, focal infection of the prostate gland is the same as that which occurs in the teeth and tonsils. Therapeutically, however, the problem is different. Removal of teeth and tonsils completely eradicates the focus of infection; in contrast, however, the most effective methods of treating the prostate gland locally accomplish varying degrees of improvement. Nevertheless, observation has shown that

the general results of treatment are satisfactory and are enduring.

A series of patients who had chronic infectious arthritis and who received treatment for a focus of infection in the prostate gland (other foci of infection were not present) obtained the following results: (1) 28 per cent were symptomatically cured; (2) 65 per cent gave evidence of marked improvement; (3) 7 per cent gave evidence of no improvement.

Before treatment is begun it is well to let the patient know that cure occurs slowly, and is difficult to achieve; that success will depend on carrying out faithfully the measures prescribed until the signs and symptoms of inflammation and infection have disappeared entirely, or, at least, until they have shown marked regression.

It is necessary to remove all other foci of infection, to give attention to the general health of the patient, who should be advised to avoid irritating and spicy foods, to correct any tendency toward constipation, and to take frequent hot baths. The patient should avoid use of alcohol and should abstain from sexual excitement and from too violent exercise. The chief measures employed locally are massage of the prostate gland and thorough irrigation of the urethra and bladder with a warm solution of potassium permanganate (1 to 8,000) or with some other mild, antiseptic solution. Massage of the prostate gland is the most valuable therapeutic measure. Massage acts chiefly by emptying the numerous follicles in which inflammatory products accumulate. It also stimulates circulation and stimulates flow of fresh blood and lymph to the inflamed gland. Massage also promotes constant absorption of toxins by the blood, thus having an effect similar to that of injection of autogenous vaccine. The interval between treatments should be two to four days. Massage should be followed by urination into a glass; in a way, this gauges the success of treatment by allowing the amount of secretion expressed to be seen and estimated. Examination of the secretion under the high power field of the microscope will indicate when the amount of pus is decreasing. Treatment should be continued until the number of pus cells is 10 or less in a high power microscopic field. Most infections require treatment for three months but some require treatment for only six or eight weeks.

COMPLICATIONS OF THE ELDERLY DIABETIC PATIENT

EDWARD H. RYNEARSON

BEFORE the discovery of insulin, care of the elderly diabetic patient was not nearly so important as it is at the present time, for there were fewer diabetic patients who lived to reach the later periods of life. In the first part of this discussion I shall review facts which are pertinent to this statement, all of which are found in more detail in the excellent presentation by Joslin, Root, and their associates.* No one should attempt to treat diabetes without familiarity with this great book. The second part of this paper will be concerned with a brief analysis of the 1,016 diabetic patients examined at The Mayo Clinic during 1936, in an effort to understand the problems presented by elderly diabetic patients.

First, then, it will be well to borrow some background material from Joslin and his associates. They emphasized the increasing importance of the problems of diabetes since they estimated that there are 300,000 mild cases, 175,000 moderately severe cases, and 25,000 severe cases of diabetes in this country. Whereas, before the discovery of insulin the diabetic patient lived for an average of only five years, he now lives for an average of eleven years and probably will live twenty to twenty-five years. The onset of diabetes is more than twice as frequent at ages of more than forty years as it is at ages less than that. These two factors, namely the lengthening life of the diabetic patient and the higher incidence of onset among individuals more than forty years of age, combine with a third factor, the aging of the population in general, to explain the increasing numbers of elderly diabetic patients. Thus, the death rate from diabetes is involving fewer young individuals

* "The treatment of diabetes mellitus."

and more elderly persons. This is well illustrated in Table 1, which is Table 6 of the sixth edition of "Diabetes Mellitus."

TABLE 1

AVERAGE DEATH-RATES FROM DIABETES IN MASSACHUSETTS AND IN THE METROPOLITAN LIFE INSURANCE COMPANY BY AGE*

Years.	Massachusetts Death-rate in age group.			Metropolitan Death-rate in age group.		
	Under 20	20-49	50 and over	Under 25	25-44	45-74
1901 to 1905	3.4	6.8	54	+	+	+
1906 to 1910	3.6	7.3	63	+	+	+
1911 to 1915	4.3	8.3	73	3.0	7.2	63.7
1916 to 1920	4.1	8.7	77	3.2	7.3	66.3
1921 to 1925	2.9	7.0	86	2.8	7.1	73.2
1926 to 1930	1.6	5.2	97	2.2	5.9	83.3
1931 to 1935	1.1	5.6	120	1.8	5.8	95.5

* Prepared with the coöperation of the Statistical Bureau of the Metropolitan Life Insurance Company.

+ Not available.

Now, in order to consider briefly a representative group of diabetic patients, I have selected all diabetic patients who registered in The Mayo Clinic during 1936. In Table 2, these patients are distributed according to their ages at onset of the disease and are subdivided into sexes, indicating the percentage of persons of each sex whose disease developed in each decade of life. It can be seen that 55.7 per cent of the entire group were males and that the greatest number of diabetic patients of both sexes became aware of the presence of the disease between the ages of forty and seventy years. Although diabetes does develop more frequently among persons of the older than of the younger age groups, the disease of older persons is usually not of the more severe type. At the Clinic we grade the severity of diabetes from 1 to 4. Diabetes of grade 1 is that which is controlled by the simple, qualitative restriction of foods which are high in content of carbohydrate. Diabetes

TABLE 2
DIABETES MELLITUS
1936
AGE AT ONSET

Age, years.	Males.		Females.		Total.	
	Patients.	Per cent.	Patients.	Per cent.	Patients.	Per cent.
0-9	20	52.6	18	47.4	38	100
10-14	9	42.9	12	57.1	21	100
15-19	13	59.1	9	40.9	22	100
20-29	42	53.8	36	46.2	78	100
30-39	57	52.8	51	47.2	108	100
40-49	145	62.2	88	37.8	233	100
50-59	150	51.2	143	48.8	293	100
60-69	98	56.0	77	44.0	175	100
70-79	26	70.3	11	29.7	37	100
80-89	2	66.7	1	33.3	3	100
Onset not stated	4	50.0	4	50.0	8	100
Total	566	55.7	450	44.3	1016	100
Mean age	47.6		46.7		47.2	

TABLE 3
DIABETES MELLITUS
1936
AGE OF PATIENTS BY GRADE OF DIABETES
AVERAGE AGE

Grade.	Male.	Female	Total
1	55.6	55.4	55.6
2	58.3	55.7	57.1
3	51.4	52.8	52.1
4	45.7	44.0	44.7
Latent or ungraded	50.4	50.3	50.4
Total	53.8	52.4	53.2

of grade 2 requires a weighed (quantitative) diet but does not require insulin. Diabetes of grades 3 and 4 requires a weighed diet and insulin; if the daily requirement of insulin is 30 units or less, the diabetes is graded 3, if more than 30 units, it is graded 4. In Table 3 the average ages of the patients with varying degrees of diabetes can be compared and it can be seen that persons of the older ages, of both sexes, have the milder diabetes. This table is of statistical interest but has little application to an individual case, since some children have mild diabetes and some elderly individuals have very severe diabetes.

Since, as has been pointed out, patients who have diabetes may live long enough to enter the later periods of life, when diseases characteristic of those periods may develop, it will be of interest to study briefly, from this standpoint, the records of patients encountered at the Clinic in 1936.

Arteriosclerosis continues to be the most serious associated condition. It is extremely difficult to establish criteria for the diagnosis of arteriosclerosis. Any single examination is inadequate, such as palpation of vessels, visual examination of the ocular fundi, roentgenograms of the extremities for calcification, studies of blood pressure, and even a combination of such studies cannot be accurate in establishing the presence or absence of arteriosclerosis in a large group of patients. At the Clinic we plan to study a large group of patients by all of these methods but we are afraid we may have difficulty in interpreting our results. However, even with present inadequate knowledge this much is certain: that arteriosclerosis is much more frequently present among diabetic than among nondiabetic patients and that this applies particularly to coronary sclerosis. Of the 1,016 cases encountered in 1936, arteriosclerosis was diagnosed in eighty-nine (8.7 per cent), hypertension in ninety-nine (9.7 per cent), coronary disease in thirty-five (3.4 per cent), gangrene of the extremities in twenty-four (2.3 per cent) and peripheral neuritis in sixty-one (6.0 per cent). Diabetic retinitis, which was reported in seventy-four cases (7.2 per cent) is found much more frequently among patients of the upper than of the lower age groups, as was observed by Wagener, Dry and Wilder in their study of 187 cases of diabetic retinitis. Only eight of their patients were less than forty years of age. They also found that 66.8 per

cent had associated hypertension and 25 per cent suffered from some involvement of the peripheral nerves.

I know of no complications which are more discouraging, both to physicians and patients, than are diabetic retinitis and neuritis. The treatment for both conditions lacks the dramatic possibilities offered by diabetic coma, for example. The patient who has diabetic retinitis has practically no chance to obtain any marked improvement and no studies or treatment, including the administration of vitamins, have helped to any great extent. Diabetic neuritis presents a discouraging picture because, although most patients do recover, yet this very painful complication lasts for many months. Joslin said that all patients recover within a year. At the Clinic we have had some patients who have had neuritis for many years and whose condition never has improved, in spite of adequate control of the diabetes, administration of vitamin and mineral supplements, efforts to improve the peripheral circulation and so on.

The most obvious manifestation of vascular involvement of the elderly diabetic patient is gangrene of the extremities, which virtually always involves the feet and thus emphasizes the important rôle of trauma and infection. Most cases of gangrene of the foot follow trauma from tight shoes; careless carving of calluses; poor efforts at cutting nails (particularly digging in the corners and developing ingrown nails); inattention to epidermophytosis, paronychia, and so forth, and allowing external trauma (such as dropping a milk can on the foot or putting the foot where a horse can step on it). Twenty-four of our 1,016 patients had gangrene of the feet and five of these died in the hospital, three following amputation, and two who were in such poor condition that amputation could not be performed. The deaths following surgical operation might not have occurred if amputation could have been performed earlier. These patients were seen after the gangrene had become extensive.

Seventy-seven (7.5 per cent) of the 1,016 patients had carcinoma or sarcoma. These malignant tumors showed no special predilection for any part of the body, occurring in twenty-seven different sites. Carcinoma is going to increase in incidence among diabetic patients because, among other reasons, diabetic patients now live long enough for carcinoma to develop.

What of the deaths among our 1,016 patients? Of those not operated on ten died. Three died of apoplexy, one of heart failure secondary to hypertension and arteriosclerosis, one of extensive cellulitis and gangrene of the arm (the patient had been in coma for nineteen hours before admission), one of hepatic insufficiency, two of coronary thrombosis, one of diabetic gangrene of the leg, and one of bronchopneumonia. The youngest patient was fifty-two years of age and the oldest, seventy-seven; the average age was 64.3 years.

For operations of one type or another, 231 patients were hospitalized, fourteen of whom died. This mortality rate of 6.1 per cent is higher than that of previous years. The deaths resulted from pneumonia, peritonitis, coronary occlusion and so forth. The youngest patient was forty-seven years of age, the oldest, seventy-seven; the average age was sixty-two years. In summary, these deaths, both "medical" and "surgical" occurred in cases in which the individuals would have been dead for many years had it not been for the advancements which have been made in the treatment of diabetes. Diabetic patients now die from the same causes found in study of comparable series of patients who do not have diabetes, but I hasten to add that the diabetic patients are more likely to die from these causes. They are more likely to acquire, and to die from, associated infections and arterial insufficiency.

What, then, is to be done about these problems of the elderly diabetic patients? The treatment of the presenting condition varies, of course, with the individual case. The treatment of diabetic coma is being discussed by Kepler and will not be dealt with here. The treatment of diabetic gangrene is managed differently by different physicians. For the purpose of creating discussion, it may be stated that the safest way to treat gangrene of a toe is to amputate the leg above the knee. That does not mean that this should be done in all cases, but if it were done, there would be the smallest number of deaths. It is true that many patients who have early gangrene of a toe, or even of part of the foot, make a complete recovery under conservative management and at the Clinic we shall not refuse to observe and treat certain patients in this manner. The fact remains, however, that although we have many successes, the patients who do not respond, and are subjected to belated amputation, are those

most likely to die. Recently we had a patient who was admitted with gangrene of one toe. He had had one leg removed here a year previously, after many months of fruitless "conservative" treatment which almost had cost him his life. When he saw gangrene beginning in the other foot he boarded a train and hurried to us requesting immediate amputation "while I'm still in good shape." This was done and his convalescence was rapid and satisfactory. Amputations of toes or portions of a foot are sometimes successful but the mortality rate attending this type of operation is greater than that following amputation of the leg. No definite rules can be made but it may safely be said that conservative treatment should not remain conservative too long and partial amputation should be performed only if the patient and his responsible relatives know of the increased risk entailed and of the possibility that a second and higher amputation may be necessary.

In so far as conservative treatment is concerned, its aim should be proper control of the diabetes, control of the infection, prevention of trauma and improvement of circulation. It should be remembered that the feet in these cases are most sensitive. Some of the feet that have been in the worst condition of any that we have seen have been those burned by strong antiseptic substances or by application of too much heat. A warm solution of half saturated solution of boric acid and half 50 per cent alcohol works satisfactorily and its application can be alternated with periods of use of mild, dry heat as applied in boxes or cradles wherein the light bulbs are kept at a safe distance from the feet. Our results with "positive-negative" pressure machines have been unsatisfactory, and there is danger in this type of treatment if the foot is infected. There is a definite place for good chiropody in caring for softened calluses, cutting the nails, treating minor infections and so forth. If it becomes apparent that conservative measures are failing, then it is better to call for a new deal and become a radical.

As a matter of fact, the best treatment for all of these unfortunate complications is their prevention. Until the question is settled regarding the possible relationship of the fat content of food to the development of arteriosclerosis, it may be better when any evidence of arteriosclerosis is detected to avoid diets

high in fat. The diet should be sufficiently low in calories to prevent obesity. If the patient needs insulin, he should use enough to keep his urine free from sugar and should test his urine regularly to make certain that he has accomplished his purpose. He should not take too much insulin, as many physicians are of the opinion that insulin reactions may predispose to the development of coronary occlusion. He must be taught that his feet are very vulnerable and he should purchase one of the standard instruction manuals for diabetic patients and familiarize himself with the details which cannot be recounted here.

In such a book he will also find a description of those measures which are so important in the prevention of infections of the skin. A carbuncle in a case of diabetes is always serious and formerly was often fatal. The word "formerly" is used by intent for within recent years the mortality rate has decreased most satisfactorily. This improvement is attributable, not only to better control of diabetes, but to the realization that the skin around a carbuncle is susceptible to trauma and that strong antiseptic substances must not be used. Joslin's group follows the procedure of making crucial incisions of generous size, followed by application of mild antiseptic substances; the attendant results are excellent. We have followed the procedure of having little, if any, surgical intervention, relying on the continuous local application of warm, moist packs, using the solution of half boric acid and half 50 per cent alcohol. With this we administer 10 c.c. of 40 per cent solution of methenamine intravenously each day until microscopic hematuria appears. We believe that these administrations exercise germicidal action at the site of the infection. Our results have been satisfactory. We have had insufficient experience with injection of sulfanilamide for any statement regarding its value in diabetic carbuncle.

In summary, the elderly diabetic patient can prevent the development of serious complications by following a diet reasonably low in its fat content, by restricting the caloric intake to prevent obesity, by keeping his urine virtually free from sugar, by avoiding severe insulin reactions, by keeping his skin scrupulously clean, by avoiding trauma of all types but with particular protection of his feet, and by frequent contacts with

his physician. The physician must rejoice in the fact that as a result of advance in knowledge it is now possible to conserve the lives of diabetic patients to the time when complications of advancing age may occur; now he must do all he can to prevent the occurrence of complications and to treat intelligently those which do occur.

POSTPARTUM HEMORRHAGE

LAWRENCE M. RANDALL

THIS term designates excessive bleeding from the genital tract after delivery of the child. The hemorrhage may arise before or after the delivery of the placenta. The exact incidence of this condition is difficult to determine but it may complicate any confinement; hence labor should always be so conducted that hemorrhage may be treated properly and promptly.

Careful studies have shown that a large group of women who did not have postpartum hemorrhage, lost, on an average, less than 300 c.c. of blood in the third stage of labor. A loss of more than 500 c.c. of blood may be considered as postpartum hemorrhage. The fact remains, however, that the loss of a given amount of blood will constitute a significant hemorrhage in one case but not in another. Some women have lost a tremendous amount of blood and lived, while others have died apparently as a result of very little bleeding. Women, therefore, differ in their ability to withstand hemorrhage. Each case will have to be judged on its merits. If a patient is bleeding during the postpartum period and if there are such general symptoms as pallor, dyspnea, increase in the rate of the pulse and a definite drop in blood pressure, one must employ treatment that might not be justifiable or necessary if these general symptoms had not appeared.

Excessive loss of blood is normally prevented by the retraction and contraction of the uterine muscle which closes the large venous sinuses that have existed in the latter months of pregnancy. Any condition which interferes with this mechanism favors postpartum hemorrhage.

ETIOLOGY

It is rather difficult to consider specifically the etiology of postpartum hemorrhage so that one may predict those cases in

which the condition will occur. I believe that more postpartum hemorrhage is caused by improper management of the third stage of labor than by any other single cause. This improper management of the third stage of labor consists chiefly in efforts to expel the placenta from the uterus before the normal mechanism of placental separation has been completed. After the second stage of labor the uterus must accommodate itself to the marked diminution of the size of the contents, and until it has done this it usually will not resume its contraction and retraction, which will finally result in separation and expulsion of the placenta. To attempt during this time to expel the placenta from the uterus will only interfere with the normal mechanism of separation and thus predispose to hemorrhage. It is no doubt a good practice to guard the fundus with the hand during the third stage of labor. This procedure, however, has one drawback and that is a tendency on the part of the guardian to massage and press too much. In many cases the behavior of the uterus may be determined by simply observing the height and size of the fundus through the abdominal wall and by observing the amount of blood being passed from the introitus. By following this procedure one is not likely to interfere unduly. The conduct of the third stage of labor immediately following the birth of the child probably has much to do with the subsequent behavior of the uterus.

It is the duty of the obstetrician to inspect carefully the secundines immediately following delivery, in order to see if they are intact. Retention of a portion of the placenta not infrequently leads to hemorrhage.

Old multiparous women are perhaps more liable to hemorrhage than are young primiparas. Fibroid changes are more likely to be seen among the former, and fibroids no doubt act as a predisposing factor by interfering with the normal contraction and retraction of the uterus. Placenta praevia may be succeeded by postpartum hemorrhage as the largest sinuses under the placenta are situated in a portion of the uterine wall in which contraction and retraction of the muscle are not efficient. Abruptio placentae is not infrequently succeeded by postpartum bleeding, particularly in cases of uteroplacental apoplexy. In such cases the only successful treatment frequently is to remove the uterus. When the separation is less tragic

or when partial premature separation has occurred, hemorrhage may not occur, or if it does occur, it may respond to the usual methods of treatment. In some cases one will obtain a history of excessive bleeding in previous labors and it is always well to heed this history. Bleeding may occur following delivery of twins or after hydramnios; such bleeding is caused by overdistention of the uterus and the inability of the uterine muscles to contract sufficiently to control the bleeding from the uterine sinuses.

Lacerations of the birth canal obviously are often associated with excessive loss of blood in the postpartum period. They are to be kept in mind whenever loss of blood is excessive or persistent. As a rule, if the bleeding ceases when the uterus is firmly contracted, hemorrhage from a laceration can be excluded. Naturally, the most common lacerations are those of the perineum, vaginal walls and uterine cervix.

CONDUCT OF THE NORMAL THIRD STAGE OF LABOR

One may determine the consistency of the uterus by palpating it through the abdominal wall. The uterus usually is firm, which indicates good muscular tone. If relaxation occurs, light massage will cause a contraction; when this occurs, stimulation should be stopped. Separation and extrusion of the placenta from the uterus is evidenced by contraction of the organ, an anteroposterior flattening, and elevation of the uterus in the abdomen. A soft distention of the lower uterine segment can be palpated. There may be an accompanying gush of dark blood from the vaginal introitus. The umbilical cord and protruding membranes will be seen to advance through the introitus of the vagina. After these signs of separation of the placenta, it is well to wait for a few moments before expressing the placenta from the vagina. This expression is performed by using the well-contracted uterus as a piston to force the placenta through the vagina to the introitus. Attempts at expression when the uterus is soft and relaxed have led to inversion of the uterus.

It has been a common practice among obstetricians for many years to administer the contents of an ampule of some form of extract of the posterior lobe of the pituitary body after the completion of the second stage of labor.

TREATMENT OF POSTPARTUM HEMORRHAGE

Strict asepsis should be employed in every labor. If it becomes necessary to invade the uterus during the postpartum period, the asepsis must be strict indeed, and it probably is well to use the additional precaution of an antiseptic solution such as merthiolate in order to cleanse the vaginal tract as thoroughly as possible. Ampules of solution of posterior pituitary and preparations of ergot should be available for immediate use. Instruments should be at hand, such as retractors, tenaculums for steadying the cervix and blunt-tipped packing forceps or a packing instrument such as a Holmes packer, for introducing a pack into the uterus. Gauze may be sterilized and carried in a container so that it may be ready for immediate use. Solutions for intravenous injection are now available in ampules and can be made ready for use in a short time. In cases of anemia and in cases in which conditions that may indicate the increased likelihood of postpartum bleeding have existed during pregnancy, it is well to determine the group of the patient's blood and the blood of her relatives in order that a suitable donor may be available.

When considerable blood is being lost during or after the third stage of labor one should immediately ascertain the reason for it. The first thought to occur is that of the condition of the uterus; hence, one almost invariably palpates the fundus of the uterus. If this is found to be relaxed, gentle but firm massage should be performed in the manner previously indicated. If the uterus responds by contraction and if the bleeding ceases, one may assume that the relaxation has been the cause of the bleeding. The uterus should then be watched with added care. If solution of posterior pituitary has not been administered previously, it should be given. Inasmuch as an anesthetic usually has been used it is often well to give all medication by hypodermic injection. The contents of one ampule of solution of posterior pituitary may suffice to control the situation. Since the recent development of more efficient preparations of ergot, these may be administered hypodermically, or if the situation permits they may be administered orally or by rectum. Should the uterus fail to respond to solution of posterior pituitary given hypodermically in a dose of 1 c.c., a dose of 2 minims (0.12 c.c.) of this preparation may

be given intravenously. Preparations of ergot that have been perfected recently may be given by intravenous injection. These cause a more efficient and prolonged uterine contraction than that obtained following injection of extract of potassium pituitary. I am reluctant to employ them when the placenta is still in the uterus.

When bleeding occurs from an atonic uterus that still contains the placenta it may be necessary to remove the placenta manually. The Credé method of expressing the retained placenta from the uterus, as one does a pit from a cherry, may be tried. I have little confidence in the method and believe that harm is often done by persistent and violent attempts at this maneuver. If the uterus is firmly contracted one may grasp it through the abdominal wall with the whole hand and attempt to squeeze the placenta out of the uterus. It is important to grasp the uterus by pushing the fingers well down behind the fundus. The thumb then lies over the anterior surface of the uterus and permits one to squeeze. If success does not come after one or two attempts the procedure should be discontinued. It is difficult to say how much time should elapse before a placenta is removed manually when bleeding persists. One hesitates to invade the uterus without a definite reason. On the other hand, this hesitancy should not defer the removal of a placenta until the condition of the patient becomes serious. Manual removal of the placenta is a major obstetric procedure. Careful aseptic preparations must be made. The patient should be redraped with sterile linen and the gown and gloves of the operator should be changed. It is well to have the material and instruments required for inserting a pack into the uterus, before starting the removal of the placenta. If full length rubber gloves are available they should be used as they provide added protection against the introduction of pathogenic organisms. Once the hand is inserted into the uterus it should not be withdrawn until the placenta has been entirely separated from the uterine wall and is ready to be delivered. As has been mentioned before, it is our practice at the St. Mary's Hospital to swab out the vagina with a liberal application of some antiseptic solution, such as merthiolate, just before introducing the hand into the vagina. The hand in the uterus searches for the edge of the placenta and carefully

dissects it loose from the uterine wall. The hand should be inserted to the fundus; should dissect both ways and should be worked upward toward the fundus; one should then dissect in one direction, as clockwise, around the cavity of the uterus. After the dissection has been continued around the circumference of the uterus and the placenta apparently has been separated, the hand should circle the uterus in a reverse direction to be sure that no cotyledons have been overlooked. The placenta and membranes are then slowly withdrawn with the hand, during a contraction of the uterus. During this procedure the outside hand aids by approximating the uterine wall to the hand that is within the uterus.

Investigation of an undelivered placenta may reveal an incarceration rather than adherence. This may be caused by atony or, more frequently, by a constriction ring at some point in the uterus. Ordinarily, gentle traction will suffice to deliver the placenta. Occasionally, the ring will need to be relaxed before the placenta can be removed. Gentle dilation may be done, but this should be done with care to avoid laceration.

It may be necessary to pack the uterus after the manual removal of the placenta or after the placenta has been delivered spontaneously or by the Credé method. We prefer iodoform gauze to the plain gauze when packing a uterus, because of the added bactericidal effect. It is probably more important to emphasize the proper method of packing the uterus than it is to quibble about the type of sterile gauze that is used. The uterus may be packed by means of the hand or a blunt packing forceps may be used, or a combination of the two methods may be employed. Some prefer to use an instrument such as the Holmes packer, devised especially for this procedure. I prefer the combination of hand and forceps. The gauze is pushed into the uterus directly from the container or from the roll held by means of a tenaculum or forceps which grasps the roll in the center, thus allowing it to unroll. The cervix is held down firmly toward the vaginal introitus by tenaculums. The gauze should not come in contact with the skin about the vulva. This area should be protected by sterile towels. When a portion of the gauze has been inserted, the gloved hand further presses it into the fundus and the cornua in order to be sure that the upper part of the uterus is snugly packed. It

does little good to pack the lower part of the uterus and then leave a space in the fundus that contains no packing, as this permits the accumulation of blood above the packing. When the uterus has been completely filled with gauze it is usually advisable to fill the vagina with gauze and then apply a vulvar pad which should be held snugly. The packing is removed at the end of twenty-four hours. If it is at all worth while to pack a uterus it should be thoroughly and completely done. Incompletely packing the uterus does little to control hemorrhage and gives a false sense of security. Bleeding may continue in spite of a properly inserted pack and the use of oxytocics. In such cases hysterectomy is to be considered.

When severe hemorrhages occur or in cases in which there is evidence of circulatory collapse after any postpartum bleeding, treatment must be instituted for this condition. The foot of the table should be elevated to lower the head below the rest of the body, and heat should be applied externally. Five to 10 minims (0.3 to 0.6 c.c.) of the solution of epinephrine hydrochloride may be administered hypodermically. The intravenous administration of fluids serves a very useful and often life-saving purpose in these cases. The immediate need is for fluid to combat the circulatory collapse. Blood is no doubt the ideal fluid but often is not immediately available and the delay necessary to obtain a suitable donor may be fatal to the patient. The intravenous injection of physiologic saline solution will at least temporarily help in counteracting the circulatory collapse. The drawback to this fluid is that it is often not retained in the circulation long enough to overcome the difficulty permanently. We have for many years resorted to the intravenous injection of a solution of acacia in physiologic saline solution and believe that this is a very valuable treatment. There are several features of this solution which recommend it for these emergencies. Solutions of acacia made in our laboratory have been used after they have been kept in the icebox for a long time. Commercial preparations which are now available can likewise be kept ready for immediate injection. It therefore is possible to prepare a solution of acacia for injection in a very few minutes. Another important advantage of the solution of acacia is that it is a fluid which is retained in the vessels. The blood pressure is quickly re-

stored to a safe level and unless further loss of blood occurs the blood pressure usually will be maintained at this level. When blood becomes available for transfusion it may safely be given after a previous injection of a solution of acacia. We have administered as much as 1,200 c.c. of this solution to a patient. In our experience no untoward reaction to this form of treatment has occurred.

If excessive bleeding occurs and does not cease when the fundus is well contracted, one should inspect the birth canal for lacerations. This inspection should be made while the vaginal canal is well exposed with retractors. In addition, the vaginal canal should be carefully palpated. Not infrequently palpation reveals a laceration that is visualized with difficulty because of the amount of hemorrhage. The vaginal wall, especially around the urethra and above the pubic rami, should be investigated. The cervix should be grasped with a tenaculum and carefully inspected in a systematic manner by proceeding from one point on the cervix entirely around the periphery until the point of departure has been reached. When a laceration is found either in the vagina or cervix it should be repaired with special care to be sure that the bleeding point has been secured. When a bleeding point is identified it is best to ligate the point separately rather than to attempt to include it in the suture that closes the laceration.

The condition of the blood should be determined during the puerperium and transfusions administered if there is sufficient anemia to justify such procedure. In many instances the use of a high vitamin diet and some preparation of iron is all that is necessary. Nursing should be encouraged unless the patient is markedly debilitated; lactation aids materially in the involution of the uterus.

TREATMENT OF POSTPARTUM THROMBOPHLEBITIS

NELSON W. BARKER AND LAWRENCE M. RANDALL

TREATMENT of thrombophlebitis which occurs in the puerperium, can be divided as follows: (1) preventive measures; (2) avoidance of pulmonary embolism; (3) management during the acute phase of the disease; (4) prevention of late effects, namely, those owing to chronic venous insufficiency of the affected limb. This paper is concerned solely with treatment of postpartum thrombophlebitis which affects the lower extremities. It is probable that a certain amount of venous thrombosis of the uterine veins occurs coincidentally with normal involution of the uterus and that it is of no clinical significance. In certain cases, particularly if puerperal sepsis and pelvic cellulitis are present, septic uterine thrombophlebitis extends to the internal iliac veins and is the source of pyemia or of infection disseminated throughout the body. In other cases, abnormally extensive thrombophlebitis involves the veins of the broad ligament, produces pelvic symptoms and can be recognized clinically. However, thrombophlebitis that involves uterine and internal iliac veins may be recognized only at necropsy.

Prevention of postpartum thrombophlebitis of the lower extremities involves consideration of the factors responsible for it. Little progress in elucidating these factors has been made in the past thirty-five years. Theoretically, as in other types of thrombophlebitis, there are three factors, namely, some local lesion of the intima of the vein, disturbance of the clotting mechanism of the blood and venous stasis. It is possible that any one of these factors, if of sufficient degree, can produce venous thrombosis but it is more probable that the condition occurs only when all factors are present in combination. There is statistical evidence that postpartum thrombophlebitis occurs more commonly following difficult labor, cesarean section and instrumental delivery during which the pelvic veins may suffer abnormal trauma which provides a locus for

development of thrombosis. Postpartum thrombophlebitis is also more common when puerperal sepsis is or has been present and, in these cases, the locus may be produced by infection. Changes in the blood itself which might render it more conducive to thrombosis have been suspected but this never has been proved. Thrombophlebitis of the veins of the leg and thigh may follow, after an interval, childbirth, surgical operation and severe injury; whichever of these is the preceding condition, the pathologic process is the same. Two common denominators of these three conditions are loss of blood and injury of tissue; these often occur at a site considerably distant from the affected vein. It seems fair to assume that in all three conditions some change occurs in the factors responsible for clotting of the blood. There also seems to be some increased tendency for thrombophlebitis to occur following severe postpartum hemorrhage as there is in other anemic states. The third factor, stasis, occurs following all deliveries as it does following surgical operations and severe injuries, inasmuch as the patient must be kept in bed for a certain period of time in the puerperium. The degree of venous stasis that occurs is undoubtedly proportional to how quietly the patient lies in bed and to the length of time that the patient stays in bed; and thus, it is proportional to the severity of the labor, the degree of operative interference and the presence of other complications. Also, venous stasis is increased if varicose veins of the legs and thighs are present and if the patient is obese. It may be increased by lowering of the arterial blood pressure such as may occur following delivery in the presence of toxemia. These factors offer some suggestions as to which cases may be more liable to complication by thrombophlebitis.

One difficulty which arises in consideration of any measure to prevent thrombophlebitis in the puerperium is that the actual incidence is quite small. Of a consecutive series of 5,724 deliveries at the Clinic, thrombophlebitis of the lower extremities which was recognized clinically occurred in only twenty cases, an incidence of slightly less than 0.4 per cent. In nine of these twenty cases of phlebitis only varices or the short saphenous vein was involved; in eleven the femoral and iliac veins were involved, and so the incidence of true phlegmasia alba dolens was only about 0.2 per cent. Thus, if any

preventive measures are instituted they would have to be carried out on 1,000 patients in order to prevent thrombophlebitis in four of them. This is an argument against adoption of any routine preventive measures the rationale of which is questionable, or employment of which is difficult, expensive or unpleasant for the patient, or of such measures as may be capable of producing some untoward effect. Only three of the twenty cases in the series mentioned were associated with uncomplicated labor. Four occurred following cesarean section, two following postpartum hemorrhage, eight following low and midforceps deliveries, two following breech delivery and one occurred following toxemia. Therefore, if one were to restrict application of measures for prevention of thrombophlebitis to patients who have the complications mentioned, these measures would be carried out unnecessarily on a much smaller number of patients than if such a restriction were not applied. Theoretically, one may say that conservatism in employment of manipulation, forceps and cesarean section would prevent occurrence of a certain small number of cases of thrombophlebitis. However, there is probably more chance for occurrence of trauma to the pelvic veins in a long and difficult labor than there is in performing a simple procedure such as low forceps delivery. It goes without saying that use of proper aseptic technic during delivery is a factor in prevention of puerperal infection and will reduce the incidence of thrombophlebitis. The factor of venous stasis occurring in the puerperium cannot be eliminated entirely but it can be reduced in many instances. It has been the policy at the Clinic for several years to have the patients move and exercise their legs as much as possible during their postpartum convalescence. This can be done without use of any complicated apparatus and, undoubtedly, it increases the rate of venous circulation.

Pulmonary embolism is always a distressing event. However, in the series of 5,724 deliveries pulmonary embolism occurred in only five cases and was fatal in only two of these instances.* Also, in four of the five cases in which it occurred,

* One of these patients was not delivered at The Mayo Clinic but was brought in on the third day following delivery; puerperal sepsis had developed; she died on the thirteenth day, four days after her temperature had become normal.

including the two fatal ones, there was no clinical evidence of thrombophlebitis of the lower extremities at any time. In the fifth case, embolism occurred one day after development of thrombophlebitis of the short saphenous vein. In cases of postoperative thrombophlebitis there is clinical and pathologic evidence to show that pulmonary embolism occurs only very early after the formation of the thrombus and we assume that this is also true in cases of postpartum thrombophlebitis. The importance of these observations is that once the clinical picture of thrombophlebitis of the leg or thigh has developed the risk of occurrence of pulmonary embolism is exceedingly small and is practically negligible after three days. Therefore, keeping such a patient in bed for an excessively long time and insisting on complete immobility of the leg in order to prevent loosening or fragmentation of the clot and migration of an embolus, in our opinion, is unnecessary and, furthermore, such forced and prolonged immobility favors occurrence of venous stasis and development of thrombosis in other veins. Also it may engender in the mind of the patient a fear complex of considerable magnitude and thus may be the starting point of a definite psychoneurosis. There is no justification for telling a patient who has thrombophlebitis that embolism may occur.

Treatment of thrombophlebitis in the acute stage involves consideration of the site and extent of the lesion. In seven of the twenty cases mentioned thrombophlebitis occurred only in a superficial varix. Such a lesion is of little clinical significance. Slight elevation of the affected limb and application of hot, wet packs to the region overlying the lesion usually will effect involution in from three to ten days. The same can be said of treatment of thrombophlebitis that involves the long or short saphenous veins, since phlebitis in either of these situations rarely, if ever, is followed by development of chronic venous insufficiency. However, as in postoperative cases, thrombophlebitis of the short saphenous vein should be watched carefully because of its tendency to extend to the femoral vein. Also, it is the type of thrombophlebitis which is most likely to be followed by pulmonary embolism at the time extension occurs.

Treatment of thrombophlebitis of the popliteal, femoral

and external iliac veins (the so-called phlegmasia alba dolens) involves consideration of other factors. It is beyond the scope of this paper to enter into the controversy as to whether the swelling and the edema of the leg associated with femoral and iliac thrombophlebitis are the result of perivenous lymphatic obstruction or are the result of extensive venous obstruction. The objective manifestations of femoral or iliac postpartum thrombophlebitis do not differ from those of postoperative, postinfectious, or posttraumatic thrombophlebitis in this particular situation. The patient may have pain of variable severity locally in the region of the involved vein and diffusely throughout the respective limb. Swelling of the leg, or both leg and thigh occurs rapidly. During the first few days the swelling is firm and brawny and does not pit. The leg often has a mottled cyanotic appearance and the superficial veins are distended and prominent. After a few days the brawny consistency gives way to a definite edema particularly below the knee and the cyanosis gradually disappears. Tenderness is practically always present over the femoral vein in the groin, frequently along Hunter's canal and usually in the popliteal space as well. The temperature may rise to 102° F. (38.9° C.). It is rarely higher than this and usually returns to normal within three or four days. A higher or more prolonged temperature should excite the suspicion that some other complication is present. The most obvious cause of the swelling and diffuse pain is venous congestion; later congestive edema occurs owing to complete obstruction of a long segment of the main venous trunk. Distention of the vein by the thrombus and periphlebitis account for the presence of local pain and tenderness. The perivenous lymphatics may be obstructed but it is impossible to account for all the signs and symptoms on the basis of lymphatic obstruction alone. One must regard acute thrombophlebitis as a pathologic lesion which has a sudden onset, produces certain physiologic disturbances and then undergoes a greater or lesser degree of involution over a period of time. It can result in a certain amount of permanent, organic damage. Part of the thrombus ultimately liquefies and disintegrates, and part of it becomes organized, as a permanent, obstructive scar. Which of these processes predominates depends on the type of lesion that is present and on the type

of reaction of the tissue of the individual to the lesion. Coincidentally, an increased load is thrown on the collateral and anastomosing veins to maintain the venous circulation of the affected limb. These collateral veins can become enlarged and fairly efficient. Efforts of therapy, therefore, during the acute stage must provide: (1) all possible aids to the venous circulation through the collateral veins; (2) aids to hasten normal involution of the lesion; (3) means for prevention of extension of thrombosis into other veins; (4) means for prevention of fear on the part of the patient. In our experience, as much can be accomplished by simple procedures as by complex methods. The affected limb should be elevated so that it forms an angle of at least 30 degrees with the horizontal. Adequate, hot, wet packs should be applied from the ankle to the groin. The technic which we have used is as follows: The skin is covered with a thin layer of petrolatum in order to prevent maceration. Over this is wrapped a thin layer of gauze. Then portions of blanket material which have been soaked in hot water and wrung out are wrapped around the leg loosely. The entire pack is surrounded by a rubber sheet and hot water bottles are placed on the outside surface of the rubber sheet in order to conserve the heat. A new pack should be applied every hour if necessary to keep it hot. Care must be taken not to have the pack hot enough to burn the skin.

Sedatives may be necessary for control of pain during the first or second day, but rarely after this. We can see no justification for use of cold packs at any time, inasmuch as application of cold produces vasoconstriction and more venous stasis than already exists; therefore, it favors extension of thrombosis to other veins and retards normal involution of the lesion. Use of dry heat has not been as successful as use of hot wet packs, although the reasons for this are not clear. A congested skin with retarded circulation is burned easily and is burned more easily by dry heat derived from electric bulbs, hot-water bottles or hot pads than by moist heat derived from hot wet packs. Rest in bed, elevation of the affected limb and application of hot wet packs are continued until swelling and edema have disappeared from the leg, until the temperature has been normal for at least four days and until tenderness along the affected veins has disappeared completely. Usually treatment

for ten to sixteen days is required to accomplish these objectives; at the end of this time the patient is allowed out of bed. We see no justification for keeping patients in bed for long periods of time, inasmuch as this does not tend to prevent pulmonary embolism, does not prevent development of chronic venous insufficiency and tends to focus the attention of the patient on the disability. Other procedures such as use of leeches, roentgen therapy, surgical enlargement of the femoral ring and splitting of the vascular sheath have been advocated for treatment of severe degrees of femoral and iliac thrombophlebitis, but there are serious objections to all these procedures. It has not been shown that they are superior in any way to the simple methods of treatment by elevation of the affected limb and application of hot packs.

One of the most important aspects of treatment of postpartum thrombophlebitis is that of management after the patient has been allowed out of bed. This is also the phase of treatment which, most likely, is neglected. During the latter days of the acute phase of the disease when the patient is yet confined to bed and the affected limb is elevated, the return circulation is adequate for this position but when the patient stands there is added to the residual partial obstruction of the femoral or iliac vein the factor of gravity. During the few ensuing weeks unless the proper measures are taken there is tremendous increase of the orthostatic venous pressure with resultant strain on the entire venous tree, development of edema and, sometimes, irreparable damage to the local venous system. If this condition is allowed to go on, secondary varices may appear and a chronic swelling of the leg may develop; also, secondary chronic lymphedema, indurated cellulitis, eczema and ulceration may develop; in other words, all the disabling complications of chronic venous insufficiency of the affected limb can occur. These complications of venous insufficiency occur notoriously in the region of the ankle and in the lower half of the leg. They practically never occur above the level of the knee or in the thigh, although slight swelling of this region can occur. The method by which chronic venous insufficiency of the limb may be prevented is by use immediately of an adequate supportive elastic bandage or elastic stocking. Inasmuch as secondary complications occurring in

the thigh are not to be feared, it is not necessary that the support extend above the knee. Furthermore, it is difficult, if not impossible, to apply a comfortable and efficient elastic support around and above the knee. Following femoral or iliac thrombophlebitis use of a heavy supportive bandage or stocking is necessary and the patient should begin to wear it when allowed out of bed for the first time. Heavy elastic stockings, if made to measure, may fit well. Measurements should be taken when the leg is free of edema. The disadvantages of elastic stockings are that they do not always fit well, cannot be readjusted once they are made, are relatively expensive and do not give adequate support after two or three months of use. Cloth mesh bandages are rarely adequate. The most efficient bandage is one made of pure solid gum rubber three inches wide and five yards long. Such a bandage should be applied over a white cotton stocking and care should be taken that the shoe overlaps completely the bandage around the heel and over the dorsum of the foot. The advantages of such a bandage are that it will control the swelling and will support the veins even after the most severe type of thrombophlebitis has occurred, that it can be applied snugly and can be adjusted for comfort; that it is relatively inexpensive and lasts a long time. The patient should be instructed regarding application of the bandage; it should be applied when the patient first gets up, should be worn continuously except when the patient is in bed at night, and should be removed and applied at noon and at 6:00 P. M. After three months the bandage or stocking may be left off half a day, later for a full day if no swelling occurs; but if some swelling does appear, use of the bandage should be continued until this no longer happens. It is rarely necessary for the patient to wear the bandage more than a year and usually not more than six months, if it is applied before any orthostatic edema has had a chance to develop. During the first few weeks, after the patient has been allowed out of bed, she should sleep with her legs elevated on one or two pillows; also, it is advisable for her to perform the so-called elevation exercises, namely, lying on the back, raising the feet in the air and going through the motions of riding a bicycle during alternate minutes for a period of fifteen or twenty minutes, twice a day. In our experience, when this

regimen is followed, the signs and symptoms of chronic venous insufficiency of the limb can be prevented even if the most severe, extensive type of postpartum iliac thrombophlebitis has occurred. For those cases of chronic venous insufficiency of the limb which are seen for the first time some years after the acute stage of thrombophlebitis occurred, treatment is the same as for chronic venous insufficiency from any other cause.

THE TREATMENT OF THE NONCONVULSIVE TOXEMIAS OF LATE PREGNANCY

ARTHUR B. HUNT

THE term "nonconvulsive toxemia of late pregnancy" has been used variously to denote the following conditions: (1) preëclampsia, or acute hypertensive toxemia, which occurs in the last weeks of gestation, and may progress to eclamptic convulsions; (2) those forms of hypertensive vascular disease or chronic nephritis which are devoid of the threat of eclamptic convulsions unless preëclampsia occurs, and (3) all toxemias of late pregnancy which are not complicated by the true convulsions, coma or pathologic findings typical of eclampsia. To avoid confusion in this paper the last meaning of the term will be used, that is, the term will be used to include all the toxemias of the latter half of gestation except eclampsia.

Without attempting to present a classification, the following nonconvulsive toxemias of late pregnancy may be listed: (1) chronic hypertensive vascular disease; (2) chronic diffuse glomerulonephritis; (3) preëclampsia; (4) the uncommon toxemias, and (5) unclassified toxemias.

CHRONIC HYPERTENSIVE VASCULAR DISEASE AND CHRONIC GLOMERULONEPHRITIS COMPLICATING PREGNANCY

The differential diagnosis of these two conditions in their early phases^{7,9} is difficult, but it is not necessary to separate these two entities in order to administer proper treatment.

Much individual judgment is required in treating these conditions. Three general guides to treatment, however, are available, namely: (1) the severity of the process, (2) the rate of progress, and (3) the time in gestation at which the toxemia appears.

In cases in which the condition is mild the values for the systolic and diastolic blood pressures do not exceed 160 mm.

and 104 mm. of mercury respectively, the edema is not marked, the urea clearance is normal and no appreciable changes are present in the ocular fundi. In such cases the pregnancy may be allowed to proceed. Ambulatory treatment should be used. The patient should receive plenty of rest and mild sedation should be employed. The diet should contain very little salt and should provide about 2,000 calories daily. The daily diet should contain 50 gm. of protein. The outlook for the fetus is rather good and the mother runs hardly any more risk than do other gravid women except that she may be left months after delivery with a varying degree of chronic hypertensive vascular disease. Therefore, it is advisable that at least eighteen months elapse before another pregnancy is allowed to occur, and even then the patient should not be allowed to become pregnant until a thorough examination of the vascular and renal systems, including such procedures as urinalysis, examination of the ocular fundi, estimation of the blood pressure, quantitative chemical analysis of the blood and determination of renal function, indicates that it is safe. If the patient has several children and if such an examination reveals the presence of a definite vascular or renal disease, contraception should be advised, but if the disease is severe and contraception seems impractical, the patient or her husband should be sterilized.

In some cases of pregnancy chronic vascular disease or chronic nephritis is present at the time of conception and the symptoms become severe early in gestation. Progression, as evidenced by severity of symptoms and changes in physical and laboratory findings, is usual. If hypertension is the only manifestation of the disease, the maternal and fetal outlook is better than it would be if other signs and symptoms were present, but if the value for the systolic blood pressure remains near 200 mm. of mercury this is not likely to be so. When such signs as increasing albuminuria, urinary casts, fixed specific gravity of the urine, edema or more than mild sclerosis of the retinal arterioles are present, abortion or induction of premature labor should be advised, as the chance of survival of the fetus is very poor and ultimate maternal risk is great. In rare cases in which children are greatly desired, one may temporize for a short time, especially if the period of viability

is near at hand. If evidence of fixed renal retention is present, termination of pregnancy is almost obligatory. In any case in which the symptoms are severe it is the duty of the physician to explain the fetal and maternal risks, both immediate and remote, to the patient and her husband. When they intelligently accept the situation, one cannot deny them some voice in making a decision.

Many follow-up studies recently have demonstrated the gravity of vascular or renal injury following all toxemias of pregnancy, including eclampsia and prolonged preëclampsia. According to Stander, in cases in which chronic glomerular nephritis or arteriosclerotic nephritis complicates pregnancy, the average mortality rate is 40 per cent within ten years after the disease is recognized. Mengert made a follow-up study in forty-five cases in which pregnancy was complicated by nephritis or essential hypertension. This study was made two and a half years after pregnancy. He found that the yearly mortality rate in these cases was 7.1 per cent. This is about twice as great as the yearly mortality rate of nephritis among women of the childbearing age who do not become pregnant, and it is eighteen times as great as the yearly death rate for women in New York City who are of childbearing age.

Even in the mild forms of toxemia the incidence of residual vascular injury has been found to be high. In 1926, Stander and Peckham recommended that the term "low reserve kidney" be used to designate mild toxemia which is easy to control and does not leave any residual injury. Peckham and Stout recently reported the results of a prolonged follow-up study of sixty-three cases in which a diagnosis of mild toxemia was well established during pregnancy. Subsequent vascular or renal involvement occurred in about 50 per cent of these cases although nearly all of the patients were normal in the puerperium. Herrick, Tillman and Grebenc noted similar findings in approximately a third of 188 cases of mild toxemia of pregnancy, which have been classified as nephritis, albuminuria of pregnancy, recurrent toxemia or low reserve kidney.

As early as 1926, Rockwood, Mussey, and Keith reported the results of a follow-up study of a series of cases in which chronic hypertension or chronic nephritis occurred during pregnancy. The chief object of this study was to determine the

subsequent morbidity and mortality. Their results and the recent advances in our knowledge of the toxemias of pregnancy explain the necessity for the radical treatment which such obstetricians as Stander, Peckham, Dieckmann,² Williams, and Mengert recently have recommended in cases of severe toxemia of pregnancy. It, therefore, is evident that examination of the patient for a prolonged period after the termination of pregnancy is an important part of the treatment of toxemia.

When the toxemia is so well established that interruption of pregnancy is indicated before viability, sterilization is desirable. Abdominal hysterectomy and salpingectomy seem preferable to the prolonged labor which follows mechanical induction of labor by such devices as a Voorhees bag. If the latter method is used, some sterilizing procedure should be employed in the puerperium. If the pregnancy is near full term, rupture of the membranes often produces satisfactory results. In many of the cases of severe toxemia the patients are elderly multiparas. In mild toxemia, spontaneous delivery may be awaited if the pregnancy is near full term. In cases in which the patient is approaching the menopause she may be sterilized with roentgen rays following delivery. Porro-Cesarean section also has a field of application, especially in cases in which leiomyomas are present in the uterus. If the husband is well advanced in age and there is small likelihood that he will remarry, vasectomy is an ideal procedure to prevent the wife from becoming pregnant again. However, at the Clinic we have found that few husbands care to submit to this procedure.

Medical treatment, which consists of rest, administration of sedatives, and a diet that is free of salt and contains only a small amount of protein (low protein diet), is helpful but not very effective in arresting the progress of the toxemia. Conservative termination of pregnancy and avoidance of repetition of the risk of gestation often are necessary. As Herrick and his associates have stated, once the definite diagnosis of chronic nephritis can be made, the safe reproductivity of the patient is at an end. In cases of chronic hypertensive vascular disease this is not always so; in fact, patients who have mild degrees of the disease very often go through pregnancy with little trouble. If the respective values for the systolic and diastolic blood pressures do not exceed 170 mm. and 110 mm.

of mercury, if the grade of albuminuria is not greater than 2, if the renal function is normal, and if the changes in the retinae are not severe or advancing, pregnancy may be continued. In these moderately severe chronic cases induction of labor at about the thirty-eighth week of gestation is often indicated for the sake of the fetus. However, if severe albuminuria, increasing sclerosis or spasm of the retinal arterioles, decreased urinary output and severe subjective symptoms such as headache, epigastric pain or visual disturbances develop, the pregnancy should be terminated.

On the other hand, as Mussey has pointed out, a past history of hypertension and albuminuria, associated perhaps with premature labor, is not definite evidence of chronic nephritis, and in some of these cases careful examination will reveal adequate arterial and renal function, so that the pregnancy may be allowed to proceed. Likewise, a history of acute nephritis or nephrosis with recovery may not mean the patient cannot well tolerate a pregnancy.

In a description of the treatment of chronic hypertensive vascular disease and chronic nephritis associated with pregnancy, there are three complications that require special consideration. These are abruptio placentae, postpartum vascular collapse, and cerebral vascular accidents and coma.

Abruptio placentae. There is more than a casual association between premature separation of the placenta and these toxemias. When this complication occurs, cesarean section is indicated only in some cases, depending on parity and the degree of separation of the placenta, or in cases in which the fetal indication is of paramount importance. In other cases, rupture of the membranes, application of an abdominal binder, and possibly the administration of small doses of pitocin (an aqueous solution containing the oxytocic principle of the posterior lobe of the pituitary body) usually prove effective. If labor is well advanced, version and extraction or forceps delivery is often possible. In event of a paralyzed (Couvelaire) uterus and postpartum hemorrhage, uterine tamponade, massive transfusions and even hysterectomy may be necessary.

Postpartum vascular collapse. In severe chronic hypertension this type of shock may follow any type of delivery within the first twelve hours. The blood pressure should, therefore,

be watched closely. The accident is rare, but it is grave unless prompt treatment is employed. Schwarz, and Adair, Hunt, and Arnell have described this condition. The latter authors have outlined an effective treatment that consists of intravenous administration of a hypertonic solution of dextrose (500 c.c. of a 20 per cent solution or 300 c.c. of a 30 per cent solution) and the administration of $\frac{3}{8}$ grain (0.024 gm.) of ephedrine by hypodermic administration. Administration of dextrose and ephedrine should be repeated as necessary to maintain the blood pressure at a sufficient level to avoid a partial anemia.

Cerebral vascular accidents and coma. In cases in which either of these complications occurs, dehydration by such measures as intravenous administration of a hypertonic solution of dextrose is worthy of trial. Induction of labor or attempts at delivery should await improvement where possible.

PREËCLAMPSIA

Prophylaxis.—The early detection and successful treatment of preëclampsia has been one of the essential aims of prenatal care. The results of this care in avoiding eclampsia nearly to the point of elimination have been brilliant. Reports of various obstetricians have been cited by Mussey and Randall and many others. Although eclampsia may intervene in spite of prenatal care, it usually is mild and the prognosis is good except in the rare cases in which it is fulminating in type and the patient lives only a few hours.

Active treatment.—In cases in which early signs of toxemia, such as mild hypertension (systolic and diastolic pressures greater than 130 mm. and 90 mm. of mercury respectively), slight albuminuria, sudden gain of weight, or edema, occur in the last trimester of pregnancy, the patients should receive close prenatal observation. Such signs are designated as "incipient toxemia." If these findings consistently are noted at repeated prenatal visits, or if they become somewhat aggravated, ambulatory treatment for mild preëclamptics should be instituted. This treatment includes: (1) the administration of sedatives, such as $\frac{1}{2}$ to $\frac{3}{4}$ grain (0.032 to 0.05 gm.) of phenobarbital sodium, or $\frac{3}{4}$ grain (0.05 gm.) of pentobarbital sodium three times daily; (2) the use of a salt-poor diet that

contains not more than 50 gm. of protein for twenty-four hours; (3) the occasional administration of mild saline laxatives, such as magnesium sulfate, and (4) frequent daily rest periods.

If the preëclampsia continues to increase in severity hospitalization should be advised.

The indication for hospitalization is the occurrence of one or more of the following signs or symptoms: (1) hypertension, that is, if the value for the systolic blood pressure varies between 150 mm. and 160 mm. of mercury or exceeds the latter figure and if the value for the diastolic pressure varies between 100 mm. and 110 mm. of mercury or exceeds 110 mm.; (2) albuminuria of grade 2 or higher (more than 20 gm. of albumin per liter of urine); (3) definite suppression of the daily output of urine; (4) marked edema; (5) progressive changes in the retina; (6) definite subjective symptoms such as headache, nervous irritability, blurring of vision and epigastric pain.

After the patient has entered the hospital the following nontherapeutic measures will serve to govern the intensity of the treatment: (1) an accurate record of the fluid intake and urinary output; (2) frequent ophthalmoscopic examination of the retina; (3) daily estimation of the blood pressure and daily urinalysis, and (4) quantitative chemical analysis of the blood.

The following principles may be employed in the treatment of preëclampsia: (1) administration of sedatives to allay generalized vascular spasm; (2) promotion of diuresis; (3) prevention or treatment of acidosis; (4) increasing the volume of blood; (5) protection of the liver; (6) attempts at rational endocrine therapy, and (7) termination of pregnancy.

At the Clinic we administer phenobarbital or pentobarbital sodium in daily doses of $1\frac{1}{2}$ to 6 grains (0.097 to 0.4 gm.) or more, as a sedative. If vomiting occurs, 2 grains (0.13 gm.) of phenobarbital sodium is administered subcutaneously every six to eight hours. If eclampsia seems imminent $\frac{1}{4}$ grain (0.016 gm.) of morphine is given when the patient is first seen. We do not use chloral hydrate because of the possibility of injury of the liver.

To promote diuresis, to protect the liver and to decrease acidosis and increase blood volume, dextrose is administered

intravenously; 500 c.c. of a 20 per cent solution usually is administered. This is not harmful when administered in moderate amounts. Higher concentrations or smaller volumes are used if oliguria is present (300 c.c. of a 30 per cent solution or 50 to 100 c.c. of a 50 per cent solution). The dextrose is given from one to three or four times a day, depending on urinary output, blood pressure and subjective symptoms. An output of at least 600 c.c. of urine in twenty-four hours is desirable. Deep intramuscular injections of magnesium sulfate (20 c.c. of a 10 per cent solution) are often used as adjunct therapy in cases in which the toxemia is severe. The intravenous method of administration of magnesium sulfate has not been used commonly at the Clinic, but McNeile, and Rucker report excellent results with it. If edema is marked but there is no appreciable acidosis, potassium chlorate or ammonium nitrate in doses of $7\frac{1}{2}$ grains (0.5 gm.) in enteric-coated capsules, twelve times a day for two or three days is administered. This method apparently produces satisfactory diuresis. Dieckmann⁴ has shown that the volume of blood is decreased in severe pre-eclampsia and eclampsia. Some obstetricians prefer to use saccharose rather than dextrose for intravenous administration in cases of preëclampsia. At the Clinic, we continue to use dextrose as the liver needs to utilize it and it usually can be administered as often as necessary. Venesection is rarely used, as it decreases the volume of the blood. It is also undesirable as the patients often have a secondary anemia.

Termination of pregnancy is the only treatment that is aimed at the cause of the disease, which is the secundines, according to our latest knowledge. If medical treatment fails labor should be induced. Failure of medical treatment is indicated by the following developments: (1) a consistent increase in the blood pressure, especially if the value for the diastolic pressure exceeds 110 mm. of mercury; (2) a urinary output which cannot be made to exceed 500 c.c. in twenty-four hours; (3) increasing arteriolar changes which result in retinitis or detachment of the retina; (4) an increase in the grade of albuminuria, casts, hematuria or edema; (5) severe subjective symptoms, and (6) prolongation of the toxemia until permanent vascular or renal injury is likely to occur (ten to forty days, depending on the severity of the toxemia).

At the Clinic, we prefer to rupture the membranes in cases in which mechanical induction of labor is indicated. This procedure, which is followed by release of amniotic fluid, may have some therapeutic value. In cases in which it cannot be employed a bag may be used. Cesarean section is reserved almost exclusively for obstetric indications such as bony dystocia; some obstetricians consider the presence of a long, uneffaced cervix, especially among elderly primiparous women, an indication for this procedure. Cesarean section when unnecessarily employed in cases of toxemia raises the maternal risk in subsequent pregnancies. Elaborate treatment or equipment need not be required for effective therapy of preëclampsia. Good results may be secured with the common sedatives, morphine and pentobarbital sodium, and intravenous administration of dextrose and rupture of the membranes. Every practitioner has the equipment for this treatment, except perhaps the apparatus for the intravenous administration of large amounts of fluid. Several reliable commercial preparations of dextrose and equipment for the administration are on the market. If such equipment is not readily at hand, slow intravenous injections of magnesium sulfate, one to three times a day (20 c.c. of 10 per cent solution with a 20 c.c. syringe) can be substituted. McNeile has administered it hourly for six doses.

ECLAMPSIA

Preëclampsia and eclampsia are one and the same disease; they are differentiated only by their severity, as evidenced by convulsions, coma or typical pathologic findings. The treatment of eclampsia is similar but more intensive than the treatment of preëclampsia, but it will not be described in this paper. Those interested in this subject are referred to such recent excellent outlines of treatment as those by Dieckmann,⁵ Rucker, and The American Committee on Maternal Welfare.

RARE NONCONVULSIVE TOXEMIAS OF PREGNANCY

These toxemias consist of acute yellow atrophy of the liver, cortical necrosis of the kidneys, lipoid nephrosis and acute nephritis complicating pregnancy. Stander and Stander and Cadden considered the first of these entities. Any parturient woman complaining of vomiting, headache or vertigo should be

hospitalized for confirmatory laboratory tests for acute yellow atrophy of the liver. Intravenous administration of rather large amounts of a solution of dextrose is the chief therapeutic procedure. Gibberd discussed cortical necrosis of the kidneys; he advised diuresis which will not be harmful to the renal parenchyma. Acute nephritis or lipoid nephrosis complicating late pregnancy often cannot be distinguished from the more common toxemias. The diagnosis and therapy for these two conditions have been described by Dieckmann³ and also by Wegner.

NONCLASSIFIED TOXEMIAS

Nonclassified toxemias of pregnancy are best treated as mild or severe preëclampsia in order to guard against the danger of eclampsia.

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CLINIC OF DR. GIRSCH D. ASTRACHAN

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THE SKIN MANIFESTATIONS IN EARLY SYPHILIS

A THOROUGH knowledge of the clinical manifestations of early syphilis facilitates the prompt diagnosis of the disease and the immediate institution of proper therapy. We understand under early syphilis, the period which elapses from the time of inoculation up to the time of the disappearance of the secondary eruption (including late secondary manifestations). It is a well-established fact, that spirochetes invade the blood stream two to three days after the inoculation, and their number is at its height in the time of the early secondary stage. Because of this, early syphilis is very infectious.

The chancre is the first recognizable syphilitic lesion, and appears on the site of inoculation. Its incubation period is from two to six weeks. It may begin with a scratch, as a superficial abrasion or a macule, which very soon develops into a papule, becomes eroded and grows larger. Chancres usually occur singly, but may appear multiple and may vary in size from a small pea-sized superficial erosion, to a hard plaque of several centimeters in diameter. The discharge from the surface of the lesion is very seldom purulent, it is more often serous in character. The clinical characteristics of the chancre depend on its location, reaction of local tissues, and the degree of secondary infection.

However, a typical chancre presents mostly a well-defined,

somewhat elevated, eroded lesion, with a hard, cartilaginous base, and is usually covered by a thin grayish membrane. It is generally indolent (unless it is complicated by mixed infection), is surrounded by a hemorrhagic line at periphery, and is almost always accompanied by induration and swelling of the adjacent lymph glands. The induration of the chancre is caused by the lymphocytic and plasma cell infiltration.



Fig. 123.—Multiple penile chancres of the prepuce. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

Chancres occur mostly on the genital organs (85–90 per cent). The common location for men is the frenulum itself or either side of it (Fig. 123).

In women, because of the relatively inaccessible character of the parts and also because the primary lesion in women is usually much smaller than in men, the genital chancre is seldom observed, the diagnosis in these cases is difficult, and the chancre often remains unnoticed by the women and also by the physician. Therefore, cases of unsuspected syphilis occur more frequently in women than in men.

Intra-urethral chancres are rare (1 to 2 per cent) but do

occur. They cause a slight serosanguineous discharge seen at the meatus and produce an induration that may be palpated through the shaft of the penis.

Syphilis d'Emblée (Syphilis without Chancre).—Cases of this kind are very rare. The infection takes place by direct inoculation of the spiròcheta into the blood, from needle pricks, transfusions, etc. Local lymphadenitis may be the only clinical symptom.

Extragenital chancres occur in 10 to 15 per cent of all cases with primary lesions. The largest majority occurs about the mouth, most often on the lips. Extragenital chancres are seen also on fingers, female breasts and nipples, eyelids, cheeks, anal region and other parts of the human body. Sometimes we see chancres in infants, who were infected by their own mothers or nurses. Kissing, sneezing, coughing, perverted sex practices, contaminated instruments, and direct contacts are the different ways of infection in cases of extra genital chancres. Among these the chancres on hands and fingers are especially important. They occur most often among physicians and dentists. Thirty-two cases are reported by Saltzman and Appelton. Most of these occurred on the left hand, because the dentists use the left hand as a guard when grinding, extracting, or retracting the cheek. Abrasion, hang nail, or fissured finger tips (novocain dermatitis) are the usual common starting points. The chancres on the fingers are sometimes very painful, may be accompanied by secondary infection and fever, are often misleading, and remain undiagnosed. Some of these chancres are operated on several times in the effort to remove the "pus." These cases often remain undiagnosed until the characteristic secondary manifestations appear.

Differential Diagnosis.—Well-developed, typical cases are very easily recognized. However, there are initial lesions which are atypical and where differential diagnosis has to be weighed and discussed.

Herpes simplex may be recognized by its acute appearance, marked edema, presence of a cluster of small vesicles on an erythematous base, accompanied by burning or itching sensations. The adjacent glands are usually not enlarged, unless the lesion becomes infected. Herpes usually heals in one to one and one-half weeks. If its involution lasts more than two

weeks, syphilis should be suspected and the necessary investigation ordered.

Chancroid presents an ulceration, acute in character, with an irregular border which is not indurated, and sometimes is undermined. The ulcer presents a purulent discharge and is accompanied by tender adenitis, which may suppurate and form a bubo. The causative agent of chancroid, the Ducrey bacillus, may be demonstrated by smear or from cultures.

Cancer may be differentiated by its pearly border, surrounded by dilated capillaries, by its readily bleeding surface, and by the late appearance of the lympho-adenopathy (after several months).

Granuloma inguinale is recognized by the absence of lymphatic involvement, slow course and by the finding of the so-called "Donovan bodies."

Lymphogranuloma inguinale (lymphopathia venereum) is differentiated from chancre by the small size and very short duration of the initial lesion, which often heals unnoticed by the patient, also by the marked swelling of the lymph glands, which are adherent to the overlying skin, become purulent, break down and finally form one or several discharging sinuses. The Frei test is always positive.

Pseudo-chancere redux is a gummatous lesion occurring at the site of a previous chancre. It is differentiated from a chancre by the marked ulceration, absence of lymphadenitis, and absence of spirochetes in the lesion.

In spite of the definite symptoms of a typical chancre, and a thorough knowledge of the differential diagnostic features by the physician, a definite diagnosis of primary syphilis should be made only by the finding of *spirocheta pallida* or by a positive serological reaction of the blood. The darkfield examination must be done several times and the serological tests repeated at least once a week for six to eight weeks before the diagnosis of syphilis is definitely excluded.

Secondary Manifestations.—About five to eight weeks after the appearance of the chancre, about the time of its disappearance and often a little before, a generalized eruption develops which is known under the term of the secondary manifestations of syphilis. This is often, but not necessarily, accompanied by constitutional symptoms like headaches, gen-

eralized adenopathy, sore throat, loss of hair, generalized weakness and anemia, low fever, "rheumatic" pains, and so on.

The rash appears at a time when spirochetes are numerous in the blood stream, when their multiplication is at its height, when foci of syphilitic infection are scattered throughout most of the body and the foundation is laid for the appearance, many years later, of serious complications of the disease.

General Characteristics.—No matter what kind of eruption any case of early syphilis presents, regardless of the duration and morphology of the eruption, every secondary syphilitic rash has certain characteristics which are observed in almost every case. They are:

(a) Almost every eruption of early syphilis is symmetrical and more or less generalized. The older the stage of syphilis is, the less symmetrical the lesions are and the eruption is more localized. Lesions of late syphilis are generally asymmetrical and mostly limited to some one location.

(b) Absence of any subjective symptoms. With the exception of very few cases, the eruption produces no itching, or painful sensations of any kind.

(c) The papular, follicular and often the pustular lesions show a definite infiltration (shottiness) which is due to the edema and lymphocytic infiltration.

(d) The color of early syphilitic lesions is not as bright and brilliant as in other dermatoses. Faint pink, dull red with a tinge of yellow or brown, is characteristic. The "raw ham" color or "copper colored spots" which are described in old textbooks as typical, while being seen in some cases, are not absolutely characteristic for early syphilis.

(e) Sequelae. It is characteristic for early syphilis that no sequelae or very insignificant ones are left after the eruption heals. The macular syphilid may heal without even the faintest trace. The papular eruption, even a very pronounced one, resolves without leaving any after-effects, except some pigmentation which may persist for some time. In rare cases a macular atrophy may appear as an after effect. The pustular lesions leave very small scars in proportion to the size of the lesions.

(f) Polymorphism. In the early stage of syphilis several

varieties of lesions are present. We often see cases in which at the same time macular, papular and sometimes even pustular lesions are seen.

(g) No matter how closely aggregated the early syphilitic lesions are, they seldom coalesce and usually remain discrete.

(h) With very few exceptions there are no vesicular syphilitic lesions in adults.

(i) The secondary syphilitic manifestations in women are much less pronounced than in men.

The cutaneous manifestations of secondary syphilis may be classified in three main groups: (1) macular, (2) papular, and (3) pustular eruptions. Very often a combination of two or three varieties may occur, so that maculopapular, papulopustular, or maculo-papulopustular eruptions may be seen.

1. **Macular Eruption** (Roseola) (Fig. 124).—This appears usually from six to eight weeks after the appearance of the chancre and presents pea- to bean-sized, well-defined spots, which are scattered mostly on the trunk, abdomen, less often on the upper and lower extremities, very seldom on the face and dorsal surface of hands and feet. The eruption is seen best below the axilla and over the shoulders. The color varies from light rose to dark brown. The eruption may disappear after a few days, or may last from one to two months; it is symmetrical and usually does not cause any symptoms. The lesions usually disappear leaving no trace, or a very slight pigmentation, or they may sometimes gradually change into papules. The roseola is often accompanied by a generalized adenopathy, mostly pronounced in the cervical and epitrochlear areas, sore throat and headaches.

The macular syphilid may sometimes be confused with drug eruptions, infectious exanthemata, tinea versicolor, pityriasis rosea, etc.

Drug eruptions are recognized by the pruritus, brighter color of the lesions, acute appearance and very often involvement of the face, and backs of hands.

The exanthemata are differentiated through the frequent elevation of the temperature, itching, and the generalization of the eruption.

Tinea versicolor is characterized by its long duration, its fawn-colored, large, irregularly shaped areas, fine scaling, and

by the demonstration of the *Microsporon furfur*. It never occurs on the face.

Pityriasis rosea is recognized by its typical oval-shaped salmon-colored, scaly lesions, the center of which is covered with finely crinkled dry epidermis, the absence of any general adenopathy and the absence of palmar and plantar lesions.

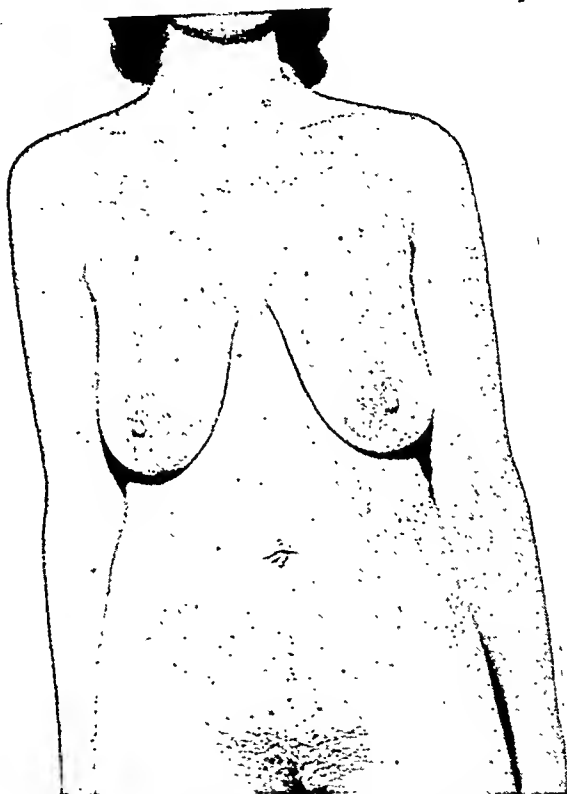


Fig. 124.—Macular syphiloderm. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

Leukoderma syphiliticum is a variety of macular syphilid, and is a late manifestation of early syphilis. A very rare form. Appears mostly half a year and later after the infection, and is usually seen on the sides of the neck in women. Sometimes it presents well-defined, round or irregularly shaped, hyperpigmented and depigmented spots, usually forming a delicate

network. Other times there are seen variously sized depigmented spots, surrounded by hyperpigmented areola. Some authors regard this disorder as an after effect of a previous roseola. This condition should be differentiated from:

Tinea versicolor which is recognized by the presence of scaling, different distribution, and demonstration of *Microsporon furfur*.

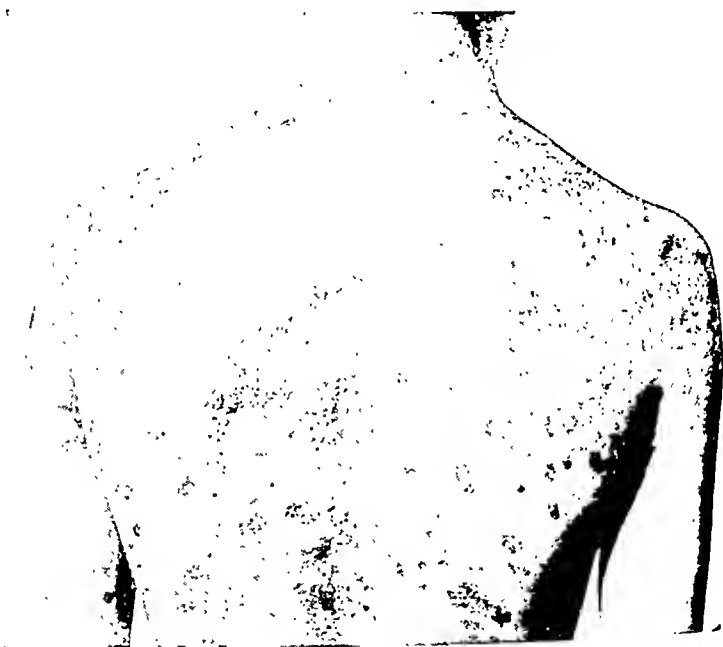


Fig. 125.—Discoid papulosquamous syphiloderm. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

Vitiligo presents larger irregularly shaped patches, which may be seen on the face and dorsi of hands. It is often asymmetrical.

Chloasma is usually located on the face (forehead) and presents large hyperpigmented patches in women with some systemic condition (uterine disturbances, pregnancy).

2. Papular Eruption.—The papular eruption is the most important and may be the first cutaneous manifestation of early syphilis. The papules may appear either alone, or with

macules. They may even be developed from earlier macules. While usually generalized, the papular eruption favors certain areas of the body, *i. e.*, face, neck, palms and soles. The individual lesion is well defined, elevated, indurated and varies in size from a pinhead to plaques 2 cm. in diameter. The lesions may have a rounded, flat, or acuminate surface and

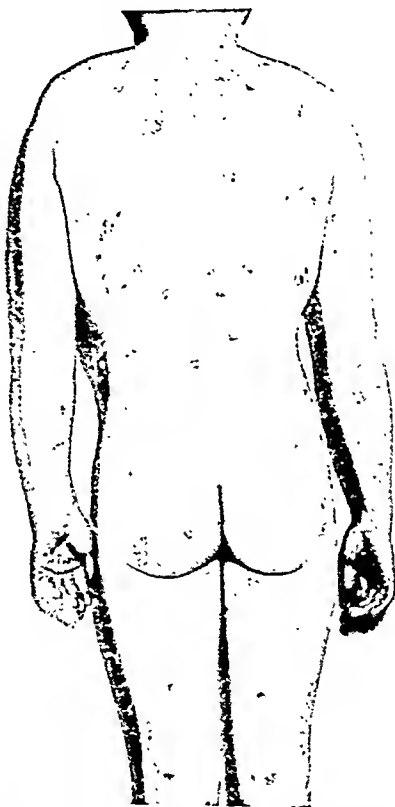


Fig. 126.—Corymbose papulosquamous syphiloderm. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

the color varies from red to dark brown. The older the papular lesion is, the darker its color and the more pronounced is the infiltration.

If the papule is small and flat, it is spoken of as *lichenoid*. If it presents some scaling, it is called *papulosquamous syphilid* (Fig. 125). Very frequently the scaling surrounds the papule,

forming a collarette. If a large papular lesion is surrounded by a group of smaller ones, this grouping is called *corymbiform syphilid* (Fig. 126). According to Stokes, Corymbose lesions in many cases occur in relapses and present a tendency toward malignant syphilis. Corymbose lesions may be disseminated among papules of other types, or occur independently. If the

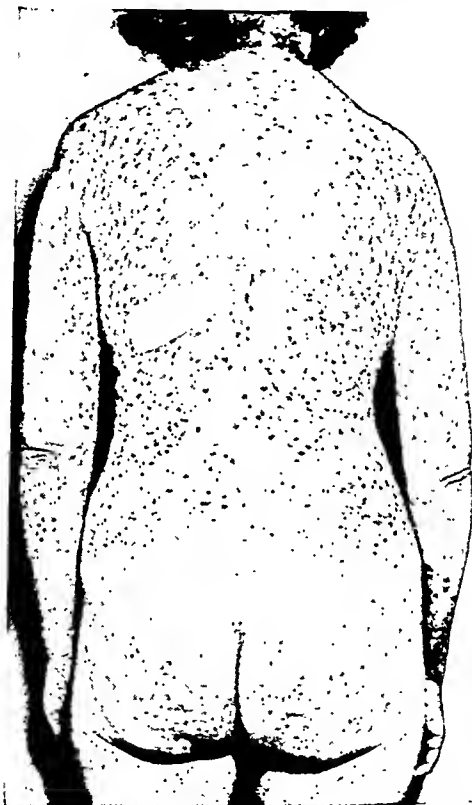


Fig. 127.—Lenticular papular syphiloderm. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

lesions are flattened, or hemispherical, pea- to fingernail-sized, they are called *lenticular* (Fig. 127). These may occur on all parts of the body, but are seen most frequently on the face (hair line on the forehead), trunk (mostly on the back), neck and about the anogenital regions. Large flat papules, varying in size from that of a dime to a quarter, present the *discoid*

variety (Fig. 125), of papular syphiloderm. They may form rings by involution of their centers. The *annular papular syphiloderm* occurs most frequently in the colored race, especially on the face. The typical lesion presents a ring with an elevated, indurated border, the surface of which tends to be smooth, shiny and sometimes slightly scaly. The center of the lesion presents either unchanged normal skin or a slight scaling. While discussing annular syphilid we have to mention the so-called *neurosyphilid of Uma* which is a recurrence and occurs several to many years after the infection. It consists of circles and semicircles with normal or pigmented centers. The border may be macular or slightly infiltrated and scaly, and is light reddish in color. The circles may form by coalescence, gyrate figures. This condition occurs chiefly on the thighs and buttocks and is resistant to treatment.

In the *differential diagnosis* of papular syphilis, several conditions have to be considered and excluded:

Psoriasis is recognized by its predilection for the extensor surfaces, bright red color of the lesions, absence of induration and the typical silvery thick scaling.

Pityriasis lichenoides chronica is recognized through its marked chronicity, elementary lesions, which is a papule showing no signs of scaling until scratched with the nail, and the absence of palmar and plantar lesions.

Lichen planus is recognized through its violaceous shiny flat papules, their small size and tendency to confluence, and absence of any scalp lesions.

Papulonecrotic tuberculid is recognized by its primary lesion, which is a papule with a dried central necrotic plug, by the presence of many pitted scars and absence of any lesions in the mouth and genitalia.

In the discussion of *papular annular syphilid* the following conditions have to be excluded:

Tinea circinata is recognized through its scaly nonindurated border, presence of minute vesicles and the demonstration of the ringworm fungus.

Erythema multiforme is recognized by its typical lesion, which is an edematous ring with a central bulla, by the presence of painful lesions in the mouth and by certain areas of predilection (extremities).

Granuloma annulare is recognized by its chronicity, and hard elevated smooth white to purplish border which is composed of closely grouped deep nodules.

In cases of *palmar or plantar syphiloderm* (Fig. 128) the following possibilities have to be excluded:

Arsenical keratosis on the palms is recognized by its pin-head-sized hard horny papules, some of which show a central depression.

Psoriasis. (See above.)

Toxic eruption is recognized through its sudden appearance, bright color of the lesion, intense pruritus.



Fig. 128.—Palmar papulosquamous syphiloderm. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

Eczema involving the palms and soles often spreads to the dorsal surfaces of hands, fingers, feet and toes. The edema and infiltration of the tissue with vesiculation and exudation also help the recognition of eczema.

The *follicular syphilid* which presents acuminate, small, firm, reddish brown papules capped by a slight scaling and situated at the mouth of the follicle occurs mostly on the back, and is accompanied, especially in older lesions, by a considerable pigmentation. On the scalp the infiltration of the hair follicle is followed by loss of hair, producing the widely and evenly disseminated moth eaten alopecia of secondary syphilis.

Several conditions have to be considered in the differential diagnosis of *follicular syphilids*:

Pityriasis rubra pilaris is recognized by its acuminate reddish papules, marked scaling on the scalp, facial seborrheic dermatitis and dark follicular horny papules occurring on the back of the fingers. Keratosis pilaris occurs more extensively on the extensor aspects of the extremities, and is of long duration.

Lichen spinulosus is recognized by its elementary lesion—long spine protruding from the follicle mouth.

Moist Papules.—These are flat, firm or soft papules, which present a grayish or brownish secreting surface. The maceration of these papules may be explained by special characteristics of their places of predilection. They are seen on parts of the body, where two cutaneous or mucocutaneous surfaces are in constant apposition and where there is hypersecretion and retention of sweat, friction and irritation.

Moist papules are seen frequently around the genitalia, anal region, and at the angles of the mouth, less often under the breasts in women, in the axillary and inguinal folds, between the toes, and in the umbilicus. A dry papule on the genitalia may be converted into an eroded moist papule by mere process of coitus, and serve as a source of infection for a healthy partner. The surface of the papule is covered by thick mucoid secretion. Because of irritation and uncleanness, moist papules around the vulva or anus may undergo papillomatous proliferation and hypertrophy, and form masses known as *condylomata lata*. These begin as a raised papule with a moist eroded surface. As the hypertrophy progresses the lesion becomes more elevated and larger. Some lesions become confluent, forming vegetating plaques, covered with grayish pellicle.

Very similar to the moist papules is the so-called *mucous patch*, which is the typical secondary syphilitic lesion of the mucous membrane. It is a raised papule whose surface has been eroded and flattened by moisture and friction, and is covered by a grayish-colored, loose or partially detached membrane. The mucous patches are seen most often in the active period of the disease on the buccal mucosa, lips near the angles of the mouth, on the tongue and tonsils, on the vulva and in the vagina. Split papules are seen at the angles of the mouth. Mucous patches are usually painless and eva-

nescent in character. They may exist sometimes only two to three days and disappear. They may stay unrecognized for a long time and are therefore very infectious. When the syphilitic papule occurs on a surface where there is constant friction, and traumatization (side of tongue), the mucous patch may become condylomatous or ulcerate. On the other hand, on the dorsum of the tongue where there is very little friction, the syphilitic lesion is not eroded, but remains a reddish smooth papule. The secretion from the moist papules, condylomata lata and mucous patches is highly infectious.

Condylomata lata have to be differentiated from the following conditions:

Condyloma acuminatum may be recognized by its cauliflower appearance, pointed top, narrow, almost pedunculated base.

Granuloma inguinale by its nodular hard border, ulcerated surface, and marked chronicity.

Pemphigus vegetans recognized by the spreading of its vegetations beyond the regions, adjacent to the mucocutaneous openings, presence of groups of blebs on the border of the plaque, and marked painfulness of the mouth lesions.

Mucous patches should be differentiated from the following conditions occurring on the mucous membrane.

Lichen planus is recognized by silvery color and punctate mosaic network of the lesion.

Erythema multiforme by its bullous lesions, mouth very sore.

Aphthae by singleness of lesions, marked soreness and presence of ulcerations.

Leukoplakia buccalis is a sharply defined, roughened and thickened patch with a dry surface; absence of any membrane or exudate.

3. Pustular Eruption.—This is relatively uncommon and occurs usually in ill-nourished persons, or individuals whose resistance has been lowered by the syphilitic process. The pustular lesions may be primary or may form from previously existing papular lesions. Some pustules may appear on the face (about the nose and forehead) and scalp, together with a generalized papular eruption.

The typical pustule is a flat, discrete, indolent, mostly pea-

sized lesion, containing very little pus but covered with a thick yellowish to brown crust. The eruption may be universal in distribution, but the face, scalp and trunk are usually the places of predilection.

Upon involution of the lesions minute pigmented or skin-colored scars or atrophic spots occur. Many of these disappear



Fig. 129.—Rupioid syphiloderm. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

later, so that the number of remaining scars is very small in proportion to the healed lesions.

The giant pustular syphilid is called rupia (Fig. 129). It appears mostly as a recurrence in neglected, untreated or insufficiently treated patients. The lesion is a moderately deep ulceration, with clear-cut edges and purulent discharge. It is covered by heavy blackish-brown crust, which thickens in the

middle by concretions from below, while the ulcer enlarges, and forms a pyramidal hardened mass of oyster-shell configuration. At times it may attain a diameter of 1 to 2 inches, and when it heals it leaves a definite characteristic pigmented scar.

Differential Diagnosis.—Several conditions should be mentioned in the differential diagnosis of pustular syphilid.

Variola pustule is umbilicated and surrounded by an inflammatory areola. The eruption presents rapid changes from papule to vesicle and pustule. It is preceded by high fever.

Drug eruptions are usually accompanied by marked subjective symptoms.

Rupoid syphilid has to be differentiated from:

Ecthyma: rarely involves face, and presents superficial ulcerations covered with a thin flat crust. Occurs mostly in undernourished children, or debilitated patients suffering from old age, poor hygiene, diabetes.

The Late Secondary Manifestations.—The skin lesions of early syphilis usually clear up in a short period and the infection enters into the so-called "latent" stage, which is asymptomatic and uneventful, and may last for many years.

However, other manifestations than those described above may appear in cases with an inborn low resistance, or those in which the natural resistance of the patient has been weakened by some chronic or acute infection, or in cases in which the gradual development of immunity is disturbed by inadequate and insufficient treatment. Some of these cases present a delayed secondary rash which lasts longer and is less amenable to therapy than the usual eruption. But the most frequent and important occurrences in these cases are the relapses on the skin, mucous membranes and viscera. These recurrences usually appear between one-half to three years after the infection, but may occur much later than that. The longer the time interval elapsing between the secondary rash and the relapse, the less widespread the relapse is. The late recurrences are apt to be less symmetrical, less generalized, more solitary; the lesions are larger and separated by wider areas of normal skin. The lesions show a tendency toward increased infiltration and are followed by marked destruction of tissue, atrophy or scar formation.

Some of these recurrences show a similarity to the early secondary eruptions, others show characteristics which make them resemble tertiary syphilis.

The recurrence of the chancre is called monorecidive. Macular, papular, pustular, follicular generalized eruptions may appear as recurrences. Many lesions have an annular configuration, some are very scaly and hyperkeratotic. Recurrent mucous patches and condylomata lata are especially dangerously infectious.

Among the late secondary eruptions the following are worth mentioning:

(1) Corymbiform syphilid. (2) Rupoid syphilid. (3) Leukoderma syphiliticum. (4) Neurosyphilid of Unna. (5) Erythema nodosum syphiliticum.

The Serology in Early Syphilis.—In spite of the definite characteristics of secondary syphilis it is desirable and imperative that the diagnosis should be verified by serological examinations.

The Wassermann test in early syphilis is positive in 36 per cent one week after the appearance of the chancre, in 60 per cent the second week, 69 per cent after the third week, and about 80 per cent after the fourth week. It is positive in no less than 98.5 per cent of all cases of secondary syphilis and in 70 to 75 per cent of all relapses.

Summary.—1. The early diagnosis of syphilis helps to prevent the infection of others, and makes the cure of the patient more certain.

2. The clinical characteristics of primary and secondary syphilis are given.

3. Differential diagnosis is discussed.

4. The recurrences are described and discussed.

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THE LATE CUTANEOUS MANIFESTATIONS OF SYPHILIS

THE late cutaneous manifestations of syphilis are being encountered with ever-decreasing frequency. Even in large clinics tertiary cutaneous syphilis is now a relative rarity. There are many factors responsible for this decrease, among the most important of which are the introduction of the arsenobenzols in the treatment of syphilis, the dissemination of knowledge of the importance of early treatment, advance in the science of serology and the establishment of more exact criteria of adequate treatment and of cure. The morbidly sensitive conscience, bred by the recent vigorous educational campaign in this country, cannot but eventually lead to a further decrease resulting in a situation wherein the late cutaneous manifestations of syphilis will be classified with the rarer dermatoses.

The diagnosis of tertiary syphilis is of importance not only because of the cutaneous manifestations per se and their progressive character, since the eruption may be minimal and may run a benign course, but because these cutaneous manifestations may only be a cloak for underlying organic involvement or implication of the cerebrospinal axis—lesions of far greater significance than the cutaneous manifestations. Statistical data show that the Wassermann test is negative in approximately 25 per cent of patients with late cutaneous manifestations of syphilis. This fact serves to indicate the importance of acquaintance with the varied clinical manifestations of tertiary syphilis of the skin and also to caution against diagnosis based wholly on the negative results of serologic tests.

The clinical picture of tertiary syphilis is not as protean as that of the secondary stage but is nevertheless very varied. In contradistinction to the acute exanthematic eruption of the secondary stage the tertiary eruption is often characterized by sparseness, lack of symmetry and the tendency to remain localized. The course is a chronic one and the development of the lesions follows a fairly definite pattern, producing characteristic formations of individual lesions. Tertiary syphilis is predominantly destructive and leads to scarring. The tertiary

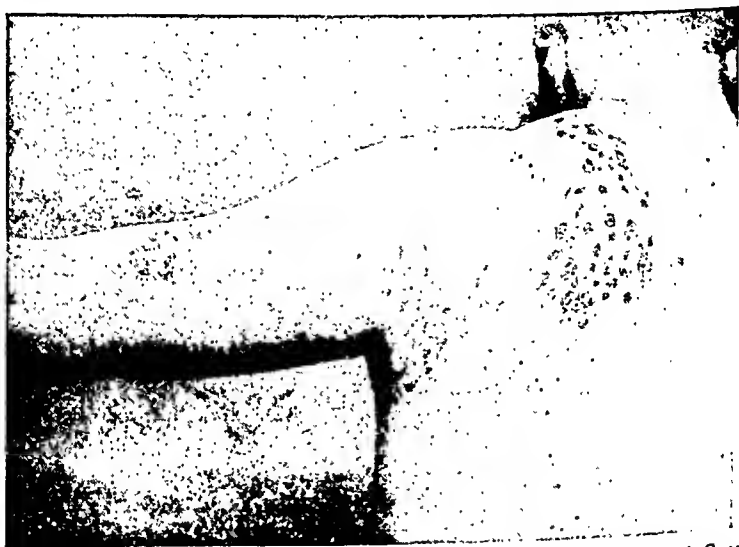


Fig. 130.—Grouped nodular syphilid. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

lesion is further characterized by an almost complete absence of spirochetes which explains its noninfectious nature.

Traditionally the late cutaneous manifestations are divided into the nodular and gummous forms. This classification is an arbitrary one and of clinical descriptive value only, since the process in each case is essentially the same. The term nodule as designated here is defined as a circumscribed infiltration of the cutis which goes on to destruction. The gumma is a destructive infiltration of the hypoderm and often occurs as a single lesion. The nodule is smaller, does not always go on to softening and ulceration, and occurs in groups, or by coales-

cence takes on the serpiginous form. It is obvious that transition forms between these two arbitrarily designated types must and do exist.

The Nodular Syphilid.—The grouped nodular syphilid may appear as early as three to five years following the infection or only after several decades. The primary lesion is a small, pale red or brownish-red, lentil-sized or larger, slightly elevated, painless, infiltrated lesion with rounded contours, which is at first shiny but which may later become scaly or even crusted. In the course of development new lesions appear peripherally while healing of the older more centrally placed lesions takes place. Peripheral spread does not proceed equally in all directions and instead of the circinate lesion so characteristic of some forms of secondary syphilis we have gyrate, polycyclic, segmented, reniform or irregularly grouped lesions. Without treatment these lesions can gradually extend to involve large parts of the cutaneous surface. As a rule there is a single localized group of nodules but lesions may also be present on other parts of the body, and when occurring in groups may, in the course of evolution, coalesce to form one large area.

On healing the lesions leave areas of mildly atrophic appearance or pale white soft smooth scars, most of them with a zone of hyperpigmentation surrounding the depigmented area. On the other hand, central healing may be so complete as to give to the whole the appearance of an eruption with peripheral lesions in which the central zone had never been involved.

The serpiginous nodular syphilid is a clinical variant of the grouped nodular variety, produced by the confluence of nodular lesions to form a band. This band is from $\frac{1}{8}$ to 1 cm. in width, erythematous or copper-colored, scaly or even crusted and extends peripherally to form horse-shoe shaped, gyrate or reniform lesions with atrophic or irregular scarred and pigmented centers. Lesions do not reappear in the scar, an important diagnostic sign in differentiating tertiary syphilis from tuberculosis of the skin, in which tubercles often reappear in the healed and scarred area. These lesions may occupy large parts of the body surface and approach or coalesce with neighboring eruptions to form bizarre or geographic figures.

Ulceration is a common accompaniment of both the above forms giving rise to the third clinical group, the ulcerative nodular and ulcerative serpiginous syphilid. For a proper understanding of the process it must be stressed that a sharp dividing line between these various forms does not exist. The crusted nodular syphilid is only a transition form between the purely nodular lesion and the frank ulceration, and lesions intermediate in character and of varying gradations between the two extremes may develop. Any combination of these various forms may exist in the same individual at one time, or at different times, or may even form component parts of the same lesion. The type of reaction is dependent upon immunobiologic factors, probably local in character, or possibly influenced by local considerations. These findings have their analogy in the tuberculids, of which several types, varying from the relatively anergic to the relatively hyperergic, may be co-existent in the one individual.

The ulceronodular lesion is characterized by a cluster of rounded ulcerations, with the punched-out appearance, perpendicular borders and infiltrated base characteristic of the syphilitic tertiary ulcerations. The floor is covered with thick sanious pus or the entire ulceration is covered with an adherent greenish-black crust. At times ostraceous crusts are formed, so called because of the many layers which constitute this crust, the oldest and smallest occupying the topmost central position. It is the result of an intermittent but progressive destructive process. Peripheral extension takes place as in the non-ulcerative variety, while healing takes place in the older more centrally placed lesions. The scars are at first brownish or of a purple hue but gradual depigmentation leaves a white smooth scar with a surrounding narrow zone of hyperpigmentation. Hypertrophic scars and true keloids occasionally result.

Ulceration is a more frequent accompaniment of the serpiginous lesion than of the nodular variety. The gyrate or reniform infiltrated border becomes hollowed out, the depth depending upon the degree of infiltration, and is similarly crust-covered or pus containing. The ulceroserpiginous lesion with its advancing gyrate ulcerated border and inner scarred

area is as characteristic a clinical picture as there is in dermatology.

The destructive effects of the ulceronodular and ulceroserpiginous varieties are, as a rule, not of great significance since the entire process is quite superficial and the deeper structures are not at all affected. Involvement of the thin mucocutaneous and orificial parts such as the nose, ears, eyelids, prepuce and vulva may however produce serious cosmetic and functional damaging effects and result in ectropion, symblepharon, narrowing of buccal orifice, etc.

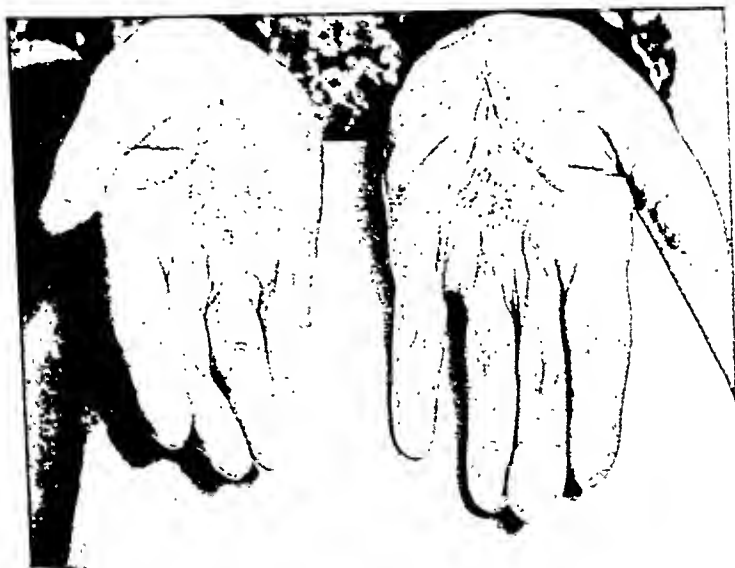


Fig. 131.—Palmar syphilid of three years' duration. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

Gumma.—The gumma has always been considered the classical lesion of tertiary cutaneous syphilis. This is based on other considerations than frequency since the nodular syphilid is more common than the gumma. It starts as a small, subcutaneous, rounded, firm, painless nodule, the size of a pea or even larger when first detected. The overlying skin is freely movable over the nodule. Early and small, it barely causes any perceptible elevation, but in the course of evolution, as the lesion continues to grow, the site becomes definitely

elevated, the overlying skin becomes adherent and of a pink, then of a livid, or violaceous color. Even at this stage the lesion may undergo complete resolution, but almost invariably the gumma goes on to softening and finally to ulceration. A thick, gummy, sanious material is released. The opening increases in size and in the fully developed stage the deep punched-out ulcer with perpendicular borders and indurated dull-red base is formed. The sites of predilection for gummas include the soft parts of the leg especially just below the knee, the thigh, the forearms, the forehead, the nose and the sternal region, but gummas may appear on any part of the body. Gummas may appear relatively early, that is, three to five years after infection. As a rule a single gumma is present but numerous gummas may appear on various parts of the body or in the same locality. Neighboring ulcerations may coalesce and be separated only by epithelial bridges which eventually also disappear and leave a single large ulceration.

The course of development extends over a relatively short period of time, several weeks to several months, and when fully developed the gumma may remain for a period of six months to two years without cicatrization. The resultant scar depends on the extent and severity of the ulceration and upon the treatment. Small lesions treated early will leave good scars with very little if any retraction and no functional disturbance. Even large ulcerations will leave surprisingly smooth flat scars. Lesions which extend deeply to involve other structures such as muscles, tendons and bone leave depressed and adherent scars which may interfere with the function of the part. Extensive gummas of the face, fortunately rare enough nowadays, may cause severe and unsightly mutilations of the nose and eyelids or even of the greater part of the face, the underlying structures and the buccal cavity.

The gumma is a painless lesion. Pain is present only in those instances in which extension of the ulceration or the resultant scar interferes with the nerve trunk. The general health of the patient remains surprisingly good, except in those in whom large parts of the cutaneous surface are involved. In the latter cachexia may supervene. Occasionally extensive and prolonged involvement will lead to generalized amyloidosis.

There is another form, a diffuse gummous infiltration which

may occupy a relatively small area or involve the greater part of an extremity. Ulceration takes place at numerous sites and destruction continues until, at times, the entire area is hollowed out. The infiltrate may be very superficial and leave a shallow ulcer or may extend deeply and produce a great deal of destruction, and finally irregularly shaped and depressed scars.

Gummas may in rare instances assume a verrucous or frambesiform appearance, the hypertrophic part either surrounding the ulcer or rising from the center of the ulcer. Lesions of this character at times offer interesting diagnostic problems.

Interference with the lymphatic circulation may lead to secondary elephantiasis of a part of an extremity. Esthiomène, chronic ulceration of the vulva associated with elephantiasis first described by Huguier in 1848, while in most instances now known to be the result of infection with the virus of lymphogranuloma venereum, is in some cases a tertiary manifestation of syphilis.

The late palmar and plantar syphilid often occurs without any other cutaneous manifestation of late syphilis. As a rule only one palm or one sole is affected, but both palms or both soles, or even all four parts may be involved. The lesion may be a single one covering the greater part of the palm or may consist of a variable number of small, dry, scaly spots, rounded or polycyclic, slightly elevated, definitely infiltrated and at times with a papular border. Ulceration occurs only very rarely. The advancing margin may spread distally to involve the palmar aspects of the fingers, proximally to the wrist or to the lateral and medial edges but rarely attacks the dorsal aspects of the hands or feet. Hyperkeratosis is at times very pronounced and is then frequently accompanied by fissuring. The hyperkeratosis in unusual cases may consist of large verrucous masses with deep fissures. The lesions are persistent and are very resistant to treatment. Psoriasis and eczema will at times closely resemble palmar syphilis and have to be excluded.

There are several other late cutaneous manifestations of importance:

Juxta-articular Nodes.—These are hard, indolent, non-inflammatory, of varying size from that of a hazel nut to a walnut, found in the vicinity of the joints, most often the

elbow. These nodes are fibrous in character and therefore if of long duration respond to treatment only very slightly if at all.

Chancre Redux.—A term which has unfortunately been promiscuously used to designate two conditions, first the recurrent chancre which is a result of insufficient treatment and then also to designate a lesion on the penis which is nothing more



Fig. 132.—Diffuse gummatous infiltrate. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

than a small gummatous ulceration. The first is a very early manifestation occurring within the first few weeks after treatment, the second a late manifestation.

Perforating Ulcer of the Foot (*Mal perforant du pied*).—This lesion is a trophoneurotic ulcer of small dimensions which occurs at the pressure points, the first and fifth metatarsophalangeal joints and the heel. It starts as a hyper-

keratotic area beneath which ulceration takes place, the central hyperkeratotic zone then being cast off, leaving a small ulcer with a surrounding area of hyperkeratosis. The ulcer is painless and is the result of pressure over an area with lessened innervation. In about 50 per cent of cases this lesion is associated with other manifestations of tabes dorsalis, the re-



Fig. 155. Nodular serpigineous syphilis. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

mainder occurring in other diseases of the spinal cord such as syringomyelia, or as an accompaniment of systemic diseases which affect the spinal cord secondarily such as diabetes, or as a result of peripheral nerve lesions as occurs in leprosy and polyneuritis. In tabes, rest and antisyphilitic treatment may bring about improvement and healing, but recurrence upon pressure takes place altogether too readily.

Treatment.—The treatment of the late cutaneous manifestations of syphilis is the treatment of syphilis in all its phases and with the many associated problems including reactions, complications, serologic response, duration of treatment and relapse. Within the confines of this paper it is impossible to discuss all these broad aspects of therapy and we shall deal



Fig. 134.—Perforating ulcers of the feet of four years' duration. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University)

only with those which have a more direct bearing on the treatment of the late cutaneous manifestations.

There is statistical evidence which bears out the previously held belief that there is a smaller incidence of serious visceral involvement and involvement of the central nervous system in patients with late cutaneous manifestations as compared with a similar untreated group without cutaneous manifestations.

The term benign therefore has a double significance when applied to the tertiary manifestations, first, that it rarely produces any serious local damage and second that serious visceral and nervous system involvement is diminished. Yet this protection is only relative since 36 per cent of the patients in Moore's series presented lesion elsewhere and in 25 per cent the associated lesion, cardiovascular, cerebrospinal, visceral or ocular, was of a more serious nature than the cutaneous lesion. Every patient must be thoroughly examined with these objectives in mind and no examination is complete without a lumbar or cisternal puncture. The treatment of the patient with syphilis of the central nervous system complicated by the existence of late cutaneous manifestations is an entirely different problem from that of the patient whose sole manifestation of syphilis is a gumma of the leg or a serpigino-ulcerous syphilid of the buttock. One is not concerned with the importance of therapeutic shock in the treatment of nodular or ulcerative syphilids but one injection of arsphenamine in a patient with undiagnosed cardiovascular syphilis may result in a fatality. Similarly the therapeutic paradox, otherwise unimportant, may become of prime importance if a cardiac lesion is discovered. The first and most important part of the treatment is, therefore, thorough examination. The more serious lesion, if discovered, will govern the considerations of treatment and relegate the cutaneous involvement to a position of secondary importance.

Treatment will also be influenced by the age of the patient, his or her general health and the presence of associated diseases. The patient with pulmonary tuberculosis will have to be carried along much more conservatively and with relatively smaller amount of arsenic and heavy metal; the patient with nephritis cannot tolerate as much heavy metal and more reliance will have to be placed on the arsenicals. Again and again it must be emphasized that so-called "routine" treatment must be adjusted to meet individual needs and requirements, and that every patient is a specific entity requiring careful study and observation.

The Wassermann test is positive in approximately 75 per cent of patients with late cutaneous manifestations, and in about two thirds of these is not reversible with treatment.

It must be stressed and the inquiring and worrisome patient must be made to understand, that the desideratum of treatment is not a reversal of the Wassermann test as it is in early syphilis where the object of treatment is cure, but is for relief from existing manifestations and for prevention of progression and relapse. Our present-day therapy leaves no hope for the biologic cure of late syphilis. Serologic cure, the reversal of the



Fig. 135.—Nodular ulcerative syphilid. (Courtesy of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.)

Wassermann test, in late syphilis is not to be aimed at. Statistical evidence shows that relapse occurs as frequently in patients who attain a reversal of the Wassermann test as in the Wassermann-fast group.

To avoid progression in latent syphilis two years of treatment with arsphenamine and a heavy metal, preferably bismuth, is considered as the optimum necessary amount. Occa-

sional rest periods between courses of treatment are prescribed during the second year. The problem of the treatment of the late cutaneous manifestations in the absence of other findings does not differ very much from that of the treatment of latent syphilis. The lesions are benign in character and respond very readily to treatment. Several injections of an arsenical or a heavy metal are sufficient to heal cutaneous involvement even if of quite large extent. The tendency to relapse or progression is however much greater in this group than in the group of latent syphilis and the treatment is therefore somewhat more strenuous. In a small series of cases Moore found that seven courses each of an arsphenamine and a heavy metal prevented relapse. Treatment should be continuous, but as in the treatment of all late syphilis, occasional short rest periods are not contraindicated. Neoarsphenamine is preferable to arsphenamine and in relatively smaller dosage than is used in the treatment of early syphilis. Because of the many advantages it possesses over mercury, bismuth has now almost universally replaced mercury. Courses of bismuth alternate with those of neoarsphenamine. Below is a suggested outline of treatment.

Weeks.	Drug.
1- 7.	Neoarsphenamine 0.45-0.6 Gm.
8- 15	Bismuth salicylate (in oil) 0.2 Gm.
16- 23	Neoarsphenamine 0.45-0.6 Gm.
24- 31	Bismuth salicylate (in oil) 0.2 Gm.
32- 39	Neoarsphenamine 0.45-0.6 Gm.
40- 47	Bismuth salicylate (in oil) 0.2 Gm.
48- 53	Neoarsphenamine 0.45-0.6 Gm.
54- 63	Bismuth salicylate (in oil) 0.2 Gm.
64- 69	Neoarsphenamine 0.45-0.6 Gm.
70- 79	Bismuth salicylate (in oil) 0.2 Gm.
80- 85	Neoarsphenamine 0.45-0.6 Gm.
86- 95	Bismuth salicylate (in oil) 0.2 Gm.
96- 101	Neoarsphenamine 0.45-0.6 Gm.
102- 112	Bismuth salicylate (in oil) 0.2 Gm.

- The recent decline in the popularity enjoyed by the iodides for so many years is largely due to the excellent results obtained from the administration of the arsphenamines and bismuth. The iodides are not spirocheticidal. Their value lies in the resolving effect they have on granulomatous tissue. Tertiary cutaneous manifestations will heal rapidly under iodide

therapy, but progression and relapse are not prevented. If used in conjunction with bismuth or arsenic the removal of the granulomatous tissue by the iodides will allow for better penetration of the more active remedies. The ease of administration, the relatively few contraindications, and the known beneficent effects are strong arguments for the continuation of iodide therapy. The average dose is 10 to 20 grains three times daily, of a concentrated aqueous solution of potassium or sodium iodide well diluted and taken one-half hour before meals. Iodides may be administered at any time during the course of treatment, but are most often prescribed during the heavy metal phase.

While specific treatment brings about rapid healing in the absence of local treatment, ulcerated lesions nevertheless require some form of protective dressing until such time as the lesions have become epithelialized. In the more exudative and purulent lesions hot wet compresses with a dilute solution of mercuric chloride (1:4000) are indicated. For the less exudative lesion 5 per cent mercurial ointment, or 5 to 10 per cent ammoniated mercury ointment, are satisfactory and promote more rapid healing.

The Wassermann test is performed at intervals during treatment but one is not to be influenced any more by the results of the serologic tests than one would be by a negative Wassermann obtained in the first few months, in the course of treatment of early syphilis.

Adequate post-treatment care requires semiannual complete physical and serologic examinations.

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SYPHILITIC JOINT DISEASE

It has frequently been said that syphilitic involvement of joints can simulate any form of arthritis, and that statement is probably true in rare instances; however, the great majority of cases fall into fairly well-defined categories and should be easily diagnosed if the possibility of syphilis is borne in mind. All the cases which we have seen fit readily into the following classification:

- I. Arthralgias.
- II. Synovitis or arthritis.
- III. Gummatous infiltration of soft tissues, cartilage or bone.
- IV. Periostitis adjacent to joints.
- V. Charcot joints.

Arthralgias.—In early syphilis 5 to 10 per cent of patients have vague joint, muscle or bone aches causing considerable discomfort, similar to the aches associated with influenza and other acute infections, but which are accompanied by no objective clinical or roentgenologic findings in the joints. While they may occur any time after the development of the chancre, they are commonest at the height of the systemic reaction during the secondary stage. As in arthralgias occurring during the course of other infectious diseases, the mechanism of the pain is unknown. A possible explanation in some cases is mild periostitis adjacent to the joints similar to that in case III but too slight to be seen roentgenographically.

Synovitis or Arthritis.—True involvement of joints with objective changes occurs very rarely in early syphilis (1 per

cent of Stokes's series¹) but occasionally in late syphilis. Probably the most frequent form is the bilateral hydrops or synovitis of the knee joints in congenital syphilitics called Clutton's joints. There is marked swelling but no redness, and local warmth, pain and tenderness are very slight. Roentgenologic study reveals nothing except synovial effusion. Aspiration of fluid is followed by rapid reaccumulation which may persist for many years² without permanent damage to the joint structures. In the few fluids which we have studied cytologically there was nothing characteristic; total leukocyte counts vary from 10,000 to 45,000 and a preponderance of lymphocytes is usually found on differential count. One fluid inoculated intratesticularly into a rabbit by one of us gave a negative result.

Synovitis identical with that of congenital syphilitics may occur in early and late acquired syphilis. In addition, a polyarticular form of joint involvement has been reported. We have never seen the latter but Chesney and his co-workers^{3,4} have described three cases in which diagnosis was unquestionable since intratesticular inoculation of rabbits with joint fluid was positive. The pain and local heat were slight in proportion to the swelling.

Diagnosis is based on the clinical features and on lack of response to antirheumatic drugs, a positive Wassermann reaction, and prompt response to antiluetic treatment. Congenital cases often show additional stigmata. Because the joint disease may follow trauma and lead to an erroneous diagnosis of traumatic synovitis, syphilis must be seriously thought of in all such cases, especially when effusion is unduly persistent.

The following report is typical of congenital syphilitic synovitis:

Case I.—P. H., a well-developed boy of eight years was referred by a physician to the hospital with the diagnosis of probable rheumatic fever. There had been bilateral swelling of the knees for six weeks. The swelling which had come on gradually was only slightly painful but interfered with walking. There was no previous or family history of rheumatic fever. The lungs and heart were normal except for a soft systolic blow at the apex and pulmonic area. The cardiac rate was normal. The liver and spleen were just palpable. Both knees showed a fusiform swelling with definite patellar click. They were slightly warm to touch and very slightly tender but not red. Motion was free except for slight pain on forced flexion. Additional findings of

significance were moderate keratitis and rhagades about the mouth, slight microcytic anemia, a normal white blood count, and a 4 plus blood Wassermann. (Subsequent examination of the patient's father revealed syphilitic aortic insufficiency, aortitis and a 4 plus Wassermann although he denied knowledge of primary or secondary manifestations.)

Each knee joint was aspirated four times with total leukocyte counts varying from 14,000 to 42,000. Differential counts showed great variation in the type of cells present. Early in the disease as high as 90 per cent of the cells were polymorphonuclear neutrophiles while a count made one month after admission revealed 16 per cent neutrophiles, 43 per cent small lymphocytes, 16 per cent monocytes, 21 per cent clasmatocytes and 4 per cent unclassified cells (supravitality stained preparation). Inoculation of this fluid intratesticularly into a rabbit was negative. Temperature never went above 100.5° F. and seldom above 100° F. Roentgen examination of the knees revealed only massive effusion. There was no response to antirheumatic drugs but the arthritis responded promptly to antisiphilic therapy.

Gummatous Involvement of Joints.—From the nature of the process it is obvious that this type of joint involvement occurs only in late syphilis. The gumma may originate in adjacent bone or soft tissues and infiltrate into the articulation, or it may arise within the joint. Roentgenograms may reveal large or small areas of bone destruction. Pain and local heat are either slight in proportion to swelling or entirely absent. As in other forms of joint syphilis the response to antiluetic treatment is prompt and striking; but, depending upon the degree of bone and cartilage destruction that has occurred prior to treatment, there may develop greater or less secondary osteoarthritis superimposed upon the damaged joint. In the same or other joints other types of involvement, such as synovitis and periostitis of adjacent bones, may occur as in the following case:

Case II.—On February 15, 1938, a sixty-seven-year-old married Italian female (R. G.) was admitted to the syphilis wards of Bellevue Hospital complaining of pain and swelling of the left sternoclavicular joint for fifteen months, and of pain in her right knee and lower thigh for twenty years. Her first four pregnancies resulted in normal, full-term children, all alive and well with negative Wassermann reactions in February, 1938. The next six pregnancies, starting in 1902, resulted in late miscarriages or stillbirths. The last two pregnancies resulted in living children, but both died within the first year of life.

The patient denied all knowledge of any signs of early syphilis and, apart from her present complaints, denied past illnesses of any consequence. On examination, however, she presented many late syphilitic lesions. Over the left sternoclavicular joint was a reddened, moderately tender swelling 6 cm. in

diameter. On the skin of the left shoulder at the outer end of the clavicle were 2 partially healed gummas. A third gumma, almost entirely healed, was found on the abdomen and scars of what were probably healed gummas were noted on the right breast and left chest. The pupils and fundi were normal. Examination of the heart showed slight enlargement; there were no murmurs and the A2 was not accentuated or ringing. The blood pressure was 120/80. The liver was felt 6 cm. below the costal margin and was nodular, but not tender; there were no signs of collateral circulation and no jaundice. There was slight tenderness of the right knee which was moderately swollen and presented a patellar click, and of the distal third of the femur. There was little or no limitation of motion. The deep reflexes were equal and active. There were no sensory changes and the Romberg was negative. Roentgen examination of the heart showed moderate enlargement in all diameters and definite dilatation of the supracardiac portion and arch of the aorta (9.5 cm.). The left clavicle showed destructive and hyperplastic changes of the inner third with almost complete destruction of the sternoclavicular joint and pathologic fracture. Further roentgen study showed marked osteoperiostitis of the lower third of the right femur and periostitis of the upper end of the right tibia. The right knee joint showed no abnormality except slight evidence of fluid. Aspiration of this joint yielded 8 cc. of fluid, slightly blood-tinged due to trauma on aspiration. Examination of the fluid showed 14,800 leukocytes of which 82 per cent were round cells.

The blood Wassermann was 4 plus. Icteric index and van den Bergh were normal. Blood count and chemical findings were normal.

Clinical diagnosis: gumma of the left sternoclavicular joint and median end of the clavicle, multiple skin gummas, probable gummas of the liver, aortitis, osteoperiostitis of the right femur, periostitis of the proximal end of the right tibia, and hydrarthrosis of the right knee.

In this case there is no doubt about the syphilitic nature of the gummatous lesion of the sternoclavicular joint and of the osteoperiostitis. The cause of the hydrarthrosis of the right knee is not as certain, but this was probably due to syphilitic synovitis.

Periostitis Adjacent to Joints.—Periostitis, although fairly common in both early and late syphilis, is not usually associated with joint pain. However, the coexistence of periostitis adjacent to joints is so closely related to joint pain in some cases that, in the absence of objective joint findings, the periostitis seems the most probable cause. This explanation appears logical since, in a joint like the knee, movement causes tension on the periosteum at the site of tendon insertions. The following is a most striking case thought to be of this type, although there is no absolute assurance that the joint pain and tenderness were on this basis:

Case III.—C. T., a twenty-eight-year-old married white woman, was transferred to the syphilis wards of Bellevue Hospital on March 2, 1936, with secondary syphilis. She had been admitted to the hospital because of supposed paralysis of both lower extremities. She had had a chronic sore throat ever since the first week of January, 1936. Starting in the latter part of January she noted progressive and rapid loss of weight, pain in both knees, wrists, forearms and left shoulder, and progressive weakness which resulted on March 2 in collapse with inability to move her lower extremities. Four weeks



Fig. 156.—Case III. Periostitis and subperiosteal rarefaction of radius.

prior to this she noted an eruption on her face. There had been amenorrhea for two months prior to admission. She had no knowledge of any genital lesion, but subsequent investigation revealed that her husband had probably had secondary syphilis in November, 1935.

The patient, weighing only 70 pounds, presented a picture of extreme asthenia with marked muscular wasting. Slight pressure over the bones of both arms and forearms revealed marked tenderness. Passive motion of both knees and of her left shoulder caused her to cry out with pain. There were about 15

rupial, crusted lesions on her face, two ulcerations on the dorsum of the tongue and several mucous patches on the buccal mucous membranes. Her pharynx, tonsils and faucæ were markedly injected. Scattered moist râles were heard in the left lung. The liver edge was palpable just below the costal margin. All deep reflexes were equal and active. Although she insisted that she was unable to move her lower extremities there was no neurological evidence of paralysis. Her inability to move her legs was attributed to muscular weakness and pain. Other findings were: heart rate, 120 to 150 per minute; temperature, on admission, 102° F.; blood Wassermann, 4 plus; icteric index and blood chemical examinations, negative; leukocyte count, 21,000 with 86 per cent polymorphonuclears; a moderate amount of albumin and a few granular casts in the urine.

During her first two weeks of hospitalization, fairly severe night sweats occurred, but chest films showed nothing suspicious of tuberculosis. Roentgenograms of the long bones gave slight but definite evidence of periostitis of both tibiae, fibulae and the right radius and ulna (Fig. 136). There were also circumscribed subperiosteal areas of rarefaction in the right radius and ulna and the head of the left humerus, and vague areas of rarefaction in the crest of the right tibia. These were interpreted as syphilitic osteoperiostitis. The skull roentgenogram showed a diffuse hyperostosis of the inner table of the frontal bones.

Institution of antisyphilitic treatment was followed by dramatic improvement. After the first treatment she was able to move her legs and sit up in bed. Within ten days all joint pain and tenderness had disappeared, although some bony tenderness of the legs and forearms persisted. She remained in the hospital until May 19, by which time her Wassermann reaction had been repeatedly negative for two weeks and roentgenograms revealed almost complete healing of the bone lesions. Treatment was continued in the clinic, the patient being probated fourteen months later with no clinical or serological relapse. Her spinal fluid was negative.

This unusual case of delayed and prolonged secondary syphilis associated with marked asthenia, muscular wasting, fever, night sweats, and amenorrhea is not unlike some of the cases of early syphilis with periostitis described by Fournier.⁵ Although osteoperiostitis has been shown by x-ray in cases of relapsing secondary syphilis, we have found records of no other case of secondary syphilis which showed the localized areas of subperiosteal rarefaction that were present in this patient.

Charcot Joints.—Ever since Charcot's original article on neurotrophic arthritis the diagnosis of Charcot joints has been relatively easy. The characteristic destructive and osteophytic changes, often described as a "bag of bones," associated with definite lesions of the nervous system, usually suffice to establish the diagnosis.

The clinical picture of Charcot joints may vary greatly, however, and the disease is still shrouded in much obscurity, both as to the nature and site of the trophic nerve centers or fibers involved and the cause initiating the trophic changes. There is at present no unanimity of opinion as to the character or site of the nerve lesions which may result in trophic changes in the joints. It is reasonably assumed that these joints are neurotrophic because they do not occur apart from demonstrable lesions of the nervous system, usually of the spinal cord. Trauma is frequently mentioned as the exciting cause but in Stokes's¹ series only 17 per cent were associated with definite trauma of the joint.

The explanation is frequently offered, but awaits scientific proof, that the ordinary wear and tear of daily activity is sufficient trauma in a partially anesthetized joint. Some individuals with severe tabes or syringomyelia escape neurotrophic joint disease in spite of proved trauma, while others develop extensive changes in joints which apparently have not been subjected to much activity. In at least two of the cases now under observation in the syphilis clinic at Bellevue Hospital, infection with a pyogenic coccus seems to have been the exciting factor. Possibly osteo-arthritis or any of the metabolic or infectious forms of arthritis may initiate the process.

Fisher⁶ suggests that the initial destructive changes in the central area of the articular cartilage may be due to syphilis itself. The suspicion that many of the neurotrophic joints observed in cases of tabes dorsalis are actually due to syphilitic infection within joints is frequently expressed, but here, again, scientific proof is lacking.

Assuming that Charcot joints are in fact neuro-arthropathies, and that any one of many causes may initiate the process, the great variety of features associated with Charcot joints is not surprising. Thus the onset in the cases we have observed in the Bellevue Hospital syphilis clinic sometimes was gradual and sometimes occurred with dramatic suddenness. There is usually some effusion into the joint at the onset, but this cannot always be demonstrated. As in the case reported below, the swelling may be due largely to effusion, but in other cases there may be marked edema or infiltration of the periarthicular tissues. In some cases an astonishing amount of joint

destruction seems to occur almost overnight. In such cases, especially if increased heat is present, infection should be suspected. Such cases appear to be the exceptions rather than the rule, however, and in the majority there is little to guide one as to the rate or duration of the progressive changes. The disease may progress to complete disintegration of the joint or remain stationary to all appearances for years. One of our patients has worked intermittently as a chauffeur and laborer for the past fifteen years with a Charcot joint of the knee without any obvious increase in the disability of the joint. Multiple Charcot joints may occur at about the same time in a tabetic patient or the destructive changes in the several joints may be separated by months or years.

Treatment is usually unsatisfactory and antisyphilitic therapy has no effect on the joint changes. The orthopedic service at Bellevue Hospital has had some success in recent years with fusion operations, especially in cases where the destructive processes have not been too great. The following case is presented as one which was accepted by the orthopedists as an ideal subject for such an operation.

Case IV.—J. L., a thirty-nine-year-old white male, was admitted to Bellevue Hospital February 21, 1938, with a swollen right knee which was moderately painful on walking. The swelling was first noted about the first week in January, 1938, and had gradually increased up to the date of admission. The pain had been about the same from the onset of the swelling. He gave a history of having injured his right knee about two years previously in a fall. This injury had kept him in bed for a week, but both the pain and swelling disappeared entirely within two weeks. He had noticed no disability in the knee from that date until early in January, 1938. No history of syphilis could be elicited. He denied all knowledge of an initial lesion or secondary syphilitic manifestations. No Wassermann had been taken to his knowledge prior to the one in Bellevue Hospital. On examination the patient was a well-developed, fairly strong, white laborer whose only presenting complaint was swelling of the right knee which was due to a marked intra-articular effusion. Most of the swelling could be accounted for by intracapsular fluid and there was relatively little periarticular infiltration. There was no increased heat in the joint and little, if any, tenderness. The patient walked with a very slight limp and there was pain only on walking for some distance. His pupils were irregular and fixed to light. There was no clinical evidence of cardiac enlargement, but the aortic second sound was accentuated and there was a systolic murmur over the aortic region. His blood pressure was 130/86. His biceps reflexes were equal and hyperactive. The knee jerks were absent as were the ankle jerks. There were no demonstrable sensory changes in the skin of either lower extremity and no loss of position or vibratory sense. Both the blood and spinal fluid Wass-

sermann tests were 4 plus in all dilutions. The colloidal gold curve was 01211000000. A teleroentgenogram of his heart showed no cardiac enlargement but there was apparent dilatation of his ascending aorta. x-Ray of his right knee showed massive effusion in the joint and suprapatellar bursa and fragmentation of the medial condyle of the femur and medial tuberosity of the tibia with some tendency to osteocondensation (Fig. 137). The x-ray interpretation was early Charcot joint. On aspiration of the joint abundant glary, amber-colored fluid was obtained. Cytologic examination of this revealed 700



FIG. 137.—Case IV. Early Charcot joint showing massive effusion and beginning disintegration.

leukocytes, 64 per cent of which were polymorphonuclear cells and 36 per cent lymphocytes. The Wassermann test of the fluid was 4 plus. The clinical diagnosis was tabes dorsalis with Charcot joint and probable syphilitic aortitis.

This case is typical of a relatively early Charcot joint with only moderate destructive changes. Extensive disintegration of a knee joint is illustrated in Fig. 138 which is a roentgenogram of another patient included for comparison with Fig. 137.

Other Forms.—As has already been mentioned, syphilis is said to simulate all varieties of arthritis. Under the names syphilitic rheumatism, acute syphilitic polyarthritis, polyarthritis luica,⁷ lues articularis praecox,⁸ and others, cases of polyarthritis more or less closely resembling rheumatic fever



Fig. 138.—Advanced Charcot joint of knee with severe disintegration of joint structures.

have been described. In all, however, joint involvement has been persistent rather than transient, the migratory character has been lacking, and there has been no response to antirheumatic drugs. Such cases are rare and, indeed, it is probable that some of the reported cases were not due to syphilis. Poly-

articular and muscle pain sometimes occurs following anti-syphilitic therapy in early syphilis and arouses speculation as to its nature. We have seen several instances of this type but there were no definite objective findings other than tenderness and we were never sure whether we were dealing with a totally unrelated complaint, arthralgias of secondary syphilis, a Herxheimer type of reaction in the joints, or a simple toxic reaction to arsenicals.

Freund,⁹ in his pathologic study, has described cases of syphilitic arthritis in which outstanding features were synovial proliferation and pannus formation of granulation tissue extending over the articular cartilages with resultant destruction of the latter. These are the important pathologic changes of rheumatoid arthritis; and one could surmise, therefore, that syphilis might simulate rheumatoid arthritis, especially if syphilitic juxta-articular nodules were present in the same patient and were taken to be rheumatoid subcutaneous nodules. However, we have never seen a case of syphilitic arthritis in which this differential diagnosis was a problem and it must be obvious that the coexistence of rheumatoid arthritis and syphilis in the same patient does not mean that one is related to the other as some of the earlier writers appear to have supposed. Indeed it is not clear that the syphilitic nature of the joint disease was established in the patients with pannus formation studied by Freund.

Lastly, it is necessary to discuss very briefly the nature of the osteo-arthritis which often is seen in syphilitic patients. Since osteo-arthritis occurs to some degree in most patients past middle life, there is no reason to suspect any relationship between them. In some patients, to be sure, syphilitic osteochondritis or synovitis may pave the way for osteo-arthritis in the same joint; but in such instances the osteo-arthritis occurs merely as a secondary effect in a joint made susceptible by previous damage.

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NEUROSYPHILIS—ITS EARLY DIAGNOSIS AND MANAGEMENT

"Know syphilis and all medicine will be opened unto you." Such were the words of that master clinician, the late Sir William Osler. That saying might well be paraphrased to read—"Know neurosyphilis and all clinical neurology will be opened unto you." Surely it is true that scarcely a sign or syndrome of organic nervous disease occurs, whether of infectious, vascular, neoplastic, degenerative or even traumatic origin, which may not have its counterpart in some manifestation of syphilis of the nervous system. Thus it comes about that neurosyphilis invariably has to be excluded in a large proportion of neuropsychiatric problems which present themselves for solution.

Syphilis is best understood by viewing it as a spirochetemia. When the central nervous system becomes invaded, as it surely will in fully 25 per cent of untreated and inadequately treated cases of early syphilis, it results in one of the various forms of neurosyphilis. Therefore it follows that prompt diagnosis and adequate treatment of early syphilis becomes the first duty of every physician as a prophylaxis against the devastating and all too frequent tragic effects of late neurosyphilis.

Of the various classifications of neurosyphilis, perhaps Moore's of Johns Hopkins is the most useful. This divides neurosyphilis into four main divisions as follows:

Meningeal Neurosyphilis.—This embraces the early manifestations of neurosyphilis which may occur during the first two years of the infection. Here is included acute syphilitic meningitis as well as that very important and all too frequently overlooked early asymptomatic neurosyphilis.

Vascular Neurosyphilis.—While this is usually a late manifestation it may be early. Localized as well as diffuse cerebral endarteritis without meningeal or parenchymatous changes occur in this form. Vascular accidents with resulting paralyses are frequent. This form is often complicated by cardiovascular disease.

Diffuse Meningovascular Neurosyphilis.—This form embraces about 15 per cent of neurosyphilis. It is a mixed form and not infrequently there are parenchymatous changes present in addition to meningeal and vascular. That very important late asymptomatic neurosyphilis is included in this group. Brain and cord gummata may be present and express themselves clinically as neoplasms. Convulsive seizures, transitory aphasia and paralyses, acute psychotic episodes in the form of confused and excited states, personality changes and a wide variety of neurological signs may be encountered.

Parenchymatous Neurosyphilis.—Here are included those late forms which result in so many personal and social tragedies—paresis, tabes, and primary optic atrophy. Approximately 10 per cent of all first admissions to the state hospital for the insane are cases of paresis.

Let us focus our attention upon the diagnosis and treatment of asymptomatic neurosyphilis—early and late. Inasmuch as all later forms of symptomatic neurosyphilis sometime pass through this form, it is most important that it be detected.

When an early case of syphilis has been under continuous treatment with the arsenicals and heavy metals for a period of eighteen months, irrespective of possible symptom-free condition of the patient and of the Wassermann reaction of the blood, lumbar puncture should be done and the spinal fluid carefully examined. If the findings are fully positive, *i. e.*, (1) Wassermann strongly positive, (2) globulin present as shown by Purdy's test, (3) cell count high, and (4) colloidal gold test high at left or in center, or if these four reactions are mildly positive, you are dealing with a case of early asymptomatic neurosyphilis. In the former instance malaria therapy should be instituted at once, followed up by chemotherapy with the arsenicals and heavy metals for eighteen months more, as a prophylactic against paresis and other severe forms of

neurosyphilis. In the latter instance, *i. e.*, when the four reactions are mildly positive, continuous treatment with arsenicals and heavy metals should be pushed for six months more, when serologic tests again should be performed. If a change for the better is found, the same treatment should be continued another year.

If no improvement has taken place, malaria therapy should be considered, followed by chemotherapy for another year.

When one comes across a case with a positive blood Wassermann which has been detected on routine examination or on suspicion of syphilis, even in absence of neurologic signs, personality changes, etc., a similar procedure should be carried out.

The early diagnosis of early symptomatic neurosyphilis should present no serious difficulties to the general practitioner if he will keep in mind the relative value of certain signs and symptoms and make a routine minimal neuropsychiatric investigation in suspicious cases.

A history of convulsive seizures occurring for the first time in an adult between the ages of twenty-five and fifty with changes in personality, as reported by relatives or friends, especially increasing and continued irritability and loss of temper, slowness in thinking, forgetfulness, change in personal habits and impairment of judgment; of vague complaints by the patient of a psychoneurotic-like character, including headaches, discomfort in head, feelings of dizziness, and pressure, hypersomnia, insomnia, vague aches and pains in the legs, digestive disturbances, fatigability, impairment of vision, difficulty in walking; the observance by the physician of a few or many of a wide variety of neurologic signs such as loss of facial expression, transient eye muscle palsies, brief aphasiae, weak spells, vasomotor disturbances, tremulous handwriting, slouchy gait, slurring and tremulous speech, tremors of tongue, fingers and facial musculature, changes in deep reflexes, either exaggerated, diminished, lost, or unequal; disturbances in coordination, unequal, uneven, and sluggish or absent pupillary reflexes, should immediately make the physician think of the possibility of neurosyphilis even in the absence of a positive history of syphilitic infection and in the presence of a negative Wassermann reaction in the blood. A spinal fluid test

should be made at once. If the four reactions are positive, especially the Wassermann and colloidal gold, a mental test should be made and all the findings carefully appraised, through which the type of neurosyphilis can be ascertained with a fair degree of certainty.

The treatment of any case of neurosyphilis should largely be an individual matter. Certain general rules can be laid down however. In our zeal to carry out adequate specific treatment, we should not neglect the various aspects of non-specific treatment, such as rest, diet, tonics when indicated and attention to the general hygienic rules of living.

A brief résumé of the proper treatment procedure in the different forms of symptomatic neurosyphilis follows:

Meningeal Neurosyphilis.—Daily intravenous injections of 0.01 succinimide of mercury should be given while the patient is quite ill. Follow this by tryparsamide 3 Gm. at five- to seven-day intervals for 12 to 16 injections, alternating with weekly intramuscular injections of 0.2 Gm. bismuth salicylate for an equal length of time. Follow this by potassium iodide orally or intravenously in larger doses. If satisfactory progress is not made, fever therapy should be considered and patient kept under continuous treatment for a period of three years at least.

Vascular Neurosyphilis.—Because of the frequently associated cardiac and aortic disease, arteriosclerosis, etc., one must exercise great caution in the specific treatment of these cases. It is usually well to commence treatment with a course of heavy metals and large doses of potassium iodide for a period of three months. Neoarsphenamine intravenously in small doses—0.1 Gm. weekly, gradually increasing to 0.3 Gm. or more until 10 to 12 have been given—should follow. Continue again with heavy metals and potassium iodide and follow again with neoarsphenamine. Keep up this treatment for at least two years with short rest periods if indicated.

Diffuse Meningovascular Neurosyphilis.—Here it is best to use old arsphenamine or silver arsphenamine and alternate with heavy metals along with potassium iodide orally or intravenously. At end of a year's treatment along these lines malaria therapy should be considered if satisfactory progress

has not been made. Follow the fever treatment with chemotherapy.

Tabes Dorsalis.—The spinal fluid will be found to be normal or nearly normal in at least 10 per cent of these cases—the so-called “burnt out tabes.” Specific treatment here is not needed. Otherwise give a course of neoarsphenamine and then heavy metals and potassium iodide as in previous group. At the end of six months give tryparsamide. If patient does not make satisfactory progress clinically or serologically, institute malarial therapy unless there are such contraindications as will later be pointed out in giving the procedure of malarial therapy. Keep patient under treatment two and one-half to three years with rest periods if indicated.

Meningo-encephalitic Lues (Paresis).—As soon as possible following the early diagnosis of this form, malarial therapy should be given. Follow this at once by a short course of neoarsphenamine to supplement the action of the quinine and for its tonic effects. Administer 6 to 10 intravenous injections of neoarsphenamine 0.3 to 0.6 Gm. Follow with tryparsamide weekly for 12 to 16 injections and alternate with 8 to 12 injections of bismuth salicylate intramuscularly. The chemotherapy should be continued without interruption for two and one-half to three years after malarial treatment.

MALARIAL TREATMENT PROCEDURE

There are certain definite contraindications to malarial therapy. Juvenile paresis and primary optic atrophy do not respond satisfactorily. In acute fulminating cases of paresis, the disease is likely to be aggravated. In cases of severe tabes with pronounced ataxia of long standing the malarial treatment is contraindicated.

Severe systemic diseases such as diabetes, hepatitis, tuberculosis, and nephritis unless the disease in question can be markedly modified by treatment, should not be chosen for malarial therapy.

Myocardial and aortic disease where there have been signs of decompensation are very poor risks and should be excluded. Even in absence of decompensation, there should be collaboration with a cardiologist when malarial therapy is given.

All these conditions should be excluded during the pre-

malarial phase of treatment and weak and anemic patients should be placed on a high caloric "anemia" diet and given a period of rest. A short course of tryparsamide is indicated for its tonic effect. Foci of infection in teeth, tonsils, sinuses, etc., should be removed. In fact everything should be done to bring the patient up to the best possible general condition before institution of the malarial therapy.

Routine urine and blood chemistry examinations are made and the patient's blood is typed, although in practice, it is but rarely that any reactions are observed if this is omitted and when they do occur they are usually mild. The patient's reaction to quinine is tested by injecting intracutaneously 0.1 cc. of a 1 per cent solution of urea quinine hydrochloride when a marked urticarial reaction will occur if there is hypersensitivity. In this event neoarsphenamine should be used to terminate the malaria.

The Malarial Period.—Tertian malaria (*Plasmodium vivax*), being the most benign form, should be used when possible. In certain malarial communities where large numbers of individuals are immune to the tertian form, the quartan malaria can be used. Two to 3 cc. of citrated malarial blood is used as a rule. Where malarial patients are available 2 to 3 cc. of blood is drawn from the donor and the recipient is inoculated with this. After careful preparation of the skin in the area of loose tissue around the angle of the scapula, the content of the syringe is emptied subcutaneously or intracutaneously. It is best to inject a portion of the content, partially withdraw the needle, and continue the injections in a spoke formation till content of syringe is emptied. This insures more possibilities of a "take."

The better the physical condition of the patient, the more prolonged the period of incubation is likely to be. In the majority of cases it will be ten to fourteen days. However, it may be only three days or it may be three weeks. Warm baths, injections of adrenalin chloride or T. A. B. vaccine may hasten the paroxysms. During the incubation period the temperature, pulse and respirations are carefully recorded every three hours. If the patient is in good condition he may be up and about the ward or room.

As soon as the fever begins the patient is put to bed. Eight

to 10 paroxysms are permitted depending upon the condition of the patient. In an emergency the malaria is terminated by 2 cc. of a 1 per cent solution of urea and quinine hydrochloride, otherwise quinine bisulfate, 10 grains three times a day, is given until blood is free from plasmodia for at least two weeks. In those few cases where quinine hypersensitivity has been detected, neoarsphenamine intravenously is used to terminate the malaria.

During the period of the paroxysms the temperature and pulse should be taken hourly and blood pressure taken daily during afebrile periods. Complete blood counts and urinary examinations should be made every second day and blood chemistry determinations once or twice weekly.

Very careful nursing should be provided. A light but nutritious diet should be given and alkaline drinks forced. The bowels should be emptied by enemata.

There are certain complications which must be carefully watched for and if any of them occur it becomes an indication for terminating the malaria in the manner mentioned, *i. e.*, by intravenous injection of 2 cc. of quinine and urea hydrochloride. The complications referred to are the following: continued high fever—above 106° F.—which does not yield to sponging, etc., shock, as evidenced by profound exhaustion, between chills; rising urea nitrogen as shown by blood chemistry tests; generalized convulsions, unless very mild; lightning pains; evidences of purpura; marked jaundice; bronchopneumonia; acute splenitis; thready pulse, cyanosis, and signs of edema, *i. e.*, cardiac decompensation; a hemoglobin which drops to below 40 with blood count of less than 2,000,000 with marked leukopenia; stupor or coma between chills; a sudden great increase of parasites in the blood.

We will now assume that our patient has been taken through 8 to 10 paroxysms and that the malaria has been terminated. He is now ready for postmalarial care and treatment. The patient is placed upon a high caloric "anemia" diet. A short course of neoarsphenamine is given partly to supplement the action of the quinine on the malaria and partly for its tonic effects as was mentioned previously. This should be followed by courses of tryparsamide, the heavy metals, and potassium iodide as likewise mentioned.

In spite of the efficacy of tryparsamide, special consideration must be given to the care of the eyes during its use. Frequent eyeground and visual field determinations are in order as well as frequent questioning of patient as to visual disturbances, such as dimness of vision, spots before eyes, etc. Any signs of a beginning optic neuritis or subjective complaints of disturbances of vision are indications for cessation of use of drug.

The limitations of space will not permit more to be said about the diagnosis and treatment of neurosyphilis. One point, however, should be stressed, *i. e.*, that no positive correlation exists between serologic negativity and clinical activity in cases of neurosyphilis. Many patients, especially with paresis, get complete symptomatic relief and apparent permanent arrest of the disease where serologic normality is apparently unobtainable. Again serologic negativity is obtained fairly frequently with no symptomatic improvement. As a consequence of this and many other factors, the treatment of neurosyphilis can never be reduced to a standardized routine and the exercise of good judgment and discretion on the part of the physician will always be needed.

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THE TREATMENT OF SYPHILIS

THIS subject obviously cannot be adequately covered in a short paper. All that can be done is to present briefly the treatment for the various stages of syphilis; and of syphilis of the special organs. This paper will be practical and can be used as a guide by those who are not syphilologists. The bibliography is sufficiently complete so that any one who is interested in any special phase of this subject can readily find the references.

EARLY SYPHILIS

The treatment of early syphilis performs a two-fold function. The first one is to obtain a greater number of cures of those affected and the second is to prevent the transmission and dissemination of the disease. The patient is spared the disastrous sequelae of late syphilis if the infection is properly managed at the beginning. The crucial phase of this disease is in the early stage. Also the best treatment for paresis, tabes, cardiovascular and visceral syphilis is their prevention by adequate modern treatment of early syphilis. It must be constantly kept in mind that the ultimate control of syphilis lies in the ability of the medical profession to lessen the contacts of the affected with those unaffected. By diplomatic approach, the physician may discover the source of the infection. Syphilis is transmitted mainly during the early stages—the time when mucosal and cutaneous lesions are swarming with *Spirochaeta pallida*.

Syphilis is being treated today mainly by general practitioners, many of whom lack proper training and experience.

The responsibility is indeed great upon the physician who is called to diagnose and treat a patient with early mucosal and cutaneous lesions. A mistake in judgment or in procedure leads to a chain of consequences involving not only the person before him, but all those he may infect and the resultant continuation of this dreaded disease.

The term "early syphilis" means in its broadest sense the first two or three years of the acquired disease. Treatment of syphilis in this period gives the highest percentage of cures.

Before treating a patient for syphilis, the diagnosis must be absolutely established. This must include: (1) Darkfield examination of the suspected lesion—repeated daily if necessary. Also darkfield examination of fluid obtained by puncturing neighboring enlarged lymph glands. If medicaments have been used, wet dressings of saline solution must be used; (2) blood Wassermann or other serologic tests must be made for the first four months varying from twice a week to once a month. A Wassermann or precipitation test may also be done on the suspected chancre fluid; (3) thorough physical and neurological examination and interpretation of findings in respect to syphilitic infections; (4) complete history, especially in reference to syphilitic contacts and the existence of other venereal diseases; (5) histologic examination of suspected lesion or lymph node if necessary.

It cannot be emphasized too greatly that carefully kept records of all findings and treatment is an essential part of the management of early syphilis. Late syphilis sometimes occurs as a result of slipshod methods employed in the examination, recording of findings and the treatment of early syphilitics.

Some physicians have advocated the use of several doses of an arsphenamine product within forty-eight hours after exposure for prophylactic purposes. It is the opinion of the writer that such treatment is detrimental. The physician is tempted to use prophylactic treatment because it is easier than to carry out tedious diagnostic procedures. The patient may have a syphilitic infection and it may be suppressed by the small amount of the arsphenamine employed only to reappear later in a more severe and more resistant form. It is agreed by many syphilographers that with the institution of early

treatment, it is possible to "cure" almost 100 per cent of patients with seronegative primary syphilis when the chancre is of less than fourteen days' duration.

Pusey has used the term "Golden Opportunity" in the treatment of syphilis. By this term is meant treatment of syphilis during the seronegative primary period. The Cooperative Clinic Group studies have shown that if treatment is begun in the seronegative stage, the proportion of cures is 71.4 per cent average. When treatment is begun in the seropositive primary stage, the proportion of cures is 50 per cent average. A clear loss of 21.4 per cent in outlook for cure. The earlier treatment is begun, the better the outlook for the patient and society.

The term "cured" is used with the understanding that the patient rids himself of all physical and serologic evidences of syphilis. Since there are no real criteria for "cured," the term cannot be used in its strict sense.

Until recently, the intermittent concurrent form of treatment was universally used. Rest periods were permitted between courses of treatment to aid the body in the elimination of toxic drugs and to ease the load on such organs as the liver and kidneys.

Extensive experience accumulated in recent years indicates that the continuous alternate treatment is favored over the intermittent method. By continuous treatment must be understood the continuous administration of one or several drugs without rest periods.

The facts from carefully compiled statistics cannot be denied. In comparing continuous with intermittent, intensive or irregular treatment. Stokes states:

"From the Cooperative Clinical Group material the statement can be made with almost axiomatic force that continuous treatment as defined, whether prolonged or brief, and practically regardless of the drugs used, is superior in its results to intermittent and other schemes of treatment. Continuous and intermittent treatments are in their turn both superior to so-called "intensive treatment" (very short arsphenamine courses); and irregular treatment stands throughout our studies as inefficient, productive of relapse and progression, fixed positive serological tests and unsatisfactory treatment

outcome. At certain points, "intensive" treatment is little better than irregular treatment. In the establishment of this contention a number of important conclusions were reached.

"Among cases treated with arsphenamine alone, before the administration of the heavy metal, the continuous method secured the reversal of the blood Wassermann reaction by the end of a year in 91.2 per cent; whereas the intermittent scheme of treatment with arsphenamine alone and rest periods of a month or more, secured only 58.5 per cent of reversals; and irregular treatment with arsphenamine alone, 9.3 per cent of Wassermann reversals to negative within a year. Essentially the same proportions appear in discussing the serological results, where arsphenamine and a heavy metal are used together or in alternation (combined treatment). Intermittent and irregular treatments are the principal sources of delayed reversals of the blood Wassermann reaction in point of time, 24 per cent of these cases requiring over two and one-half years to reverse under irregular, 4 per cent under intermittent, and only 1.5 per cent under continuous treatment. Essentially similar conclusions appear from the study of fixed positive serological cases, delayed reversals and serological relapses."

The League of Nations Investigation and Report on Treatment of Early Syphilis which appeared in the Journal of the American Medical Association on April 13, 1935, states that there is not enough evidence on hand to enable a clear decision to be made as to the relative merits of intermittent and continuous treatment. Both plans of treatment are outlined. Other observers such as MacKee and Rosen advocate the intermittent method using the arsphenamine and bismuth simultaneously. Perhaps a combination of the intermittent and the continuous plan may yield the best clinical and serologic results. Hoffmann employs a "maximum course system" which permits the administration of 0.45 Gm. and then 0.6 Gm. of neo- or sodium salvarsan for the first two doses followed by two weekly injections of 0.6 Gm. each. Ten to 12 injections constitute one course of treatment. Bismuth is given at the same time. Two to three courses of treatment are given with a rest period of four to five weeks between courses.

It is necessary that the patient knows at the beginning the

necessity of prolonged treatment and its cost. His chances of cure should not be jeopardized by inadequate treatment.

There are many arguments against the routinization of any treatment. In the case of early syphilis, a routine method of treatment can be recommended and followed with few exceptions. In late syphilis, individualization of treatment is absolutely essential. As a rule, early syphilis is found in young adults free from syphilitic involvement of important viscera and free of degenerating and sclerotic diseases of advancing years. Therefore, a routine plan of treatment is applicable to all patients with uncomplicated early syphilis. There is no simple plan of treatment that is universally accepted. The plan which I shall outline is in my opinion a practical one, and is the one advocated by leading American syphilographers.

The drugs that are commonly used for the treatment of early syphilis are arsphenamine, neoarsphenamine, silver arsphenamine, mapharsen, bismuth, and mercury.

Arsphenamine (606) is given to an average adult in doses of 0.2 to 0.4 Gm. The drug is diluted in the proportion of 0.1 Gm. to 20 cc. of sterile triple distilled water. The solution must be neutralized and must be given intravenously, preferably by the gravity method. It is generally agreed that arsphenamine is the most efficacious drug in the treatment of syphilis. At least 20 injections of this drug are required to cure early syphilis.

Neoarsphenamine (914) is also given intravenously in doses of 0.3 to 0.6 Gm. It is not so efficacious as arsphenamine and does not have to be neutralized. It can be diluted in half the quantity of sterile triple distilled water required for arsphenamine. The syringe method may be used.

Silver arsphenamine is given intravenously in doses of 0.1 to 0.3 Gm. It is diluted in the proportion of 0.1 Gm. to 25 cc. of sterile triple distilled water. The danger of argyria following prolonged treatment must be borne in mind.

Sulfarsphenamine is given intramuscularly in doses of 0.3 to 0.6 Gm. The total dose is dissolved in 1 to 2 cc. of sterile triple distilled water.

Tryparsamide is given intravenously in doses of 0.5 to 3 Gm. The total dose is dissolved in 10 to 20 cc. of sterile triple distilled water.

SCHEME OF TREATMENT FOR EARLY SYPHILIS .

Day or week.	Neosarsphenamine, Gm.	Interim treatment.	Blood Wassermann test.	Comment.
Day 1	0.3 to 0.45		1	Arsphenamine may be used, maximum 0.3 Gm. female to 0.4 Gm. male; mapharsen may be used in maximum 0.04 Gm. female to 0.06 Gm. male; spirochetes disappear from lesions in 24 to 48 hours; Wassermann reaction often negative by end of first course; do a lumbar puncture in this course of treatment; the first bismuth is given with the last arsenical injection.
5	0.45 to 0.6			
10	0.45 to 0.6			
Weeks 3	0.6			
4	0.6			
5	0.6			
6	0.6			
7	0.6			
8	0.6			
9	0.6			
10	0.6	Bismuth salicylate 0.2 Gm., 6 doses, 1 a week.	1	Wassermann tests first day and fifth day after arsenical.
11				
12				
13				
14				
15				
16	0.6		1	
17	0.6			
18	0.6			
19	0.6			
20	0.6			Provocative Wassermann.
21	0.6			
22	0.6			
23	0.6			
24	0.6			
25	0.6	Bismuth salicylate 0.2 Gm., 8 doses, 1 a week.	1	
26 to 33				
34	0.6		1	
35	0.6			
36	0.6			
37	0.6			
38	0.6			Patients with seronegative primary syphilis cease treatment if Wassermann always negative, after this course of bismuth; provocative Wassermann.
39	0.6			
40	0.6			
41	0.6			
42	0.6			
43	0.6	Bismuth salicylate 0.2 Gm., 10 injections, 1 a week.	1	
44 to 54				
55	0.6		1	
56	0.6			
57	0.6			
58	0.6			
59	0.6			
60	0.6			
61	0.6			
62	0.6			
63	0.6			
64	0.6		1	

Day or week.	Neoarsphenamine, Gm.	Interim treatment.	Blood Wassermann test.	Comment.
65 to 74		Bismuth salicylate 0.2 Gm. 10 injections, 1 a week.		Seropositive primary and secondary syphilis, if all signs and symptoms negative 1 year, may be put on probation.
75 to 123		No treatment.		Blood Wassermann every month or two.
123		Complete check-up, physical examination; lumbar puncture; fluoroscopic examination of cardiovascular stripe; if both lumbar punctures are negative, no repetition required; physical examination every year and Wassermann, for a few years, every six months, and thereafter along with physical examination.		

Bismarsen combines both the effects of bismuth and arsenic in one preparation. O'Leary, Stokes, and others have pointed out that it is not so efficient as the older arsphenamines in the treatment of early syphilis.

Mapharsen is administered intravenously in doses of 0.03 to 0.06 Gm., dissolved in 5 to 10 cc. of distilled water. It is the most recent of the arsenical preparations and may be used in place of the arsphenamines. According to reports published by Foerster, Astrachan and others, this drug is of low toxicity and produces good clinical results. The dissolved drug is injected rapidly into the vein.

Bismuth is used intramuscularly. A soluble or an insoluble bismuth preparation may be used. The insoluble bismuth preparation (bismuth salicylate suspended in oil) is preferred because of its slow absorption and its sustained effect after discontinuing its administration. The average adult dose is 2 grains. If a soluble bismuth preparation is desired, thio-bismol (3 grains), iodobismitol (2 cc.) or bismuth sodium tartrate (0.5 grain) may be used two or three times a week intramuscularly. Bismuth has largely replaced mercury. For best therapeutic results, the arsphenamines should be used in conjunction with bismuth.

Mercury. The insoluble mercurial preparations which are generally used are the salicylates and the soluble preparations are the bichloride and the succinimide. The insoluble prepa-

rations are preferred especially if the injections cannot be given frequently. These preparations are administered intramuscularly. Mercury rubs are seldom used.

Potassium iodide is still a valuable drug in the treatment of late syphilis. The drug may be administered by mouth in doses of 10 to 30 minims of a saturated solution three times a day. Some recommend even higher doses. Sodium iodide has been used intravenously in 15-grain doses for some of the neurological manifestations of syphilis.

The plan of treatment recommended by the author for early syphilis is the following: Arsphenamine or neoarsphenamine and insoluble bismuth are given alternately and continuously until at least 20 to 40 injections of each are given. Treatment should be continued for one year after all clinical and serological signs of syphilis have disappeared. Blood Wassermann tests are made at the beginning and end of each course of treatment. Also, a blood Wassermann test should be performed the first and fifth days after the first arsphenamine injection. Blood Wassermann tests should be made every six months for many years after cessation of treatment. Spinal fluid examination is made at the end of the first course of arsphenamine and again at the end of the second year's treatment. A complete physical and neurological examination is made including examination of the eyegrounds, visual fields, fluoroscopic and radiologic examination of the heart and great vessels. This is repeated every six months for many years.

The outline of treatment for early syphilis (pp. 1300-1301) is taken from an article by H. N. Cole which appeared in the *Journal of the American Medical Association*, December 26, 1936, and is appended for purposes of convenience.

LATENT SYPHILIS

It must be understood that in this group are included only those patients with nonrecognizable syphilitic infection and with negative spinal fluid. Diagnosis is made on history and positive blood Wassermann reaction.

The treatment of latent syphilis differs markedly from that of early syphilis. In this stage, the object of treatment is to arrest the process and control infection. Frequently, the blood Wassermann reaction remains positive even after intensive

treatment. Patients with positive blood Wassermann reactions are too often treated indefinitely with the consequence that positive damage is suffered by the viscera by the administration of antisyphilitic drugs. The treatment during this stage is more individualized. Routinization is discarded. Many problems arise which require special attention. Therefore, the plan outlined in this paper for the treatment of latent syphilis is not applicable to all cases and must be modified to meet the individual problems. In this stage, the continuous method of treatment is not essential. A combination of continuous and intermittent treatment is preferred.

The patient is given a thorough and complete physical and neurological examination including a lumbar puncture before treatment is begun. If the infection is present less than four years a plan of treatment such as given for early syphilis is pursued.

If the latency is late (over four years) 10 to 12 weekly injections of bismuth are given followed by 8 weekly injections of neoarsphenamine (not over 0.6 Gm.). This course is repeated three times during the first year without rest periods. Potassium iodide is given by mouth during the time when bismuth is being administered.

During the second year, three courses of bismuth of 10 injections each may be given with rest periods of ten weeks between courses. If the patient presents late tertiary syphilis, it is advisable to repeat the second course during the third year. If tertiary syphilitic lesions should be resistant to this form of treatment, it is necessary to substitute arsphenamine for neoarsphenamine during the first year. Potassium iodide may be given during the rest periods. On completion of this treatment, the patient is instructed to return every six months for physical and laboratory check-up. It must be understood that if the patient is in poor general health, such intensive treatment must not be administered. It may be possible to use only injections of bismuth. Rosen prefers to start the treatment of latent syphilis by the preliminary administration of a course of 10 to 12 injections of bismuth and then giving concurrently arsenic and bismuth with rest periods of four to eight weeks between courses.

CARDIOVASCULAR SYPHILIS

Treatment of cardiovascular syphilis requires the combined knowledge possessed by an internist and a syphilologist. This manifestation of syphilis, therefore, should be treated by one capable of following the clinical progress of these special organs. The Cooperative Clinical Group has shown that about 75 per cent of patients with cardiovascular syphilis had been untreated for their syphilis. It is therefore obvious that the best treatment for this phase of the disease is prophylaxis—continuous treatment of early syphilis.

Few patients tolerate the arsphenamines. Soluble bismuth given two or three times a week or insoluble bismuth given once a week often give patients symptomatic relief. Small courses are given with long intervals of rest. Neoarsphenamine in 0.05 Gm. to 0.1 Gm. or even 0.2 Gm. doses may be cautiously administered to patients with slight involvement who are compensating well in courses of 8 doses *only after having previously administered 1 or 2 courses of bismuth*. The arsphenamines are very dangerous to this class of patients. Slight Herxheimer or nitritoid reactions may terminate fatally. Most patients get along better without arsenotherapy. Iodides are sometimes very valuable in these cases. It may be necessary to continue treatment more or less indefinitely. Bed rest and digitalis are often necessary. Extreme care to avoid reactions is imperative. Vigorous treatment is never advised.

CENTRAL NERVOUS SYSTEM SYPHILIS

It is not within the scope of this paper to outline a treatment suitable for every phase of central nervous system syphilis. Every patient is a problem unto himself and at times the disease will test the knowledge and ingenuity of the physician at every turn. The outcome of the particular case cannot be foretold. Some will respond satisfactorily and others will remain resistant.

An early case of neurosyphilis that has not had adequate treatment can be treated by the administration of continuous and alternating courses of neoarsphenamine and bismuth salicylate in oil. At least 4 courses of neoarsphenamine and 8 courses of bismuth should be given. The treatment may be started with either bismuth or neoarsphenamine. Each course

of bismuth consists of 12 injections administered once a week and each course of neoarsphenamine consists of 8 injections, each given once a week. Larger doses of neoarsphenamine are tolerated by these patients, therefore maximum doses of 0.6 Gm. are given. The progress of the disease can be best studied by the Wassermann reactions of the spinal fluid. A lumbar puncture is done two to four times a year.

If at the end of the year, the spinal fluid reaction persists in remaining positive, then nonspecific heat therapy may be resorted to. The best method is malarial therapy according to O'Leary and to comparative studies made by Epstein, Solomon and Kopp and others. After the patient has had a series of 10 to 12 chills, antimalarial therapy is instituted. As soon as the patient has sufficiently recovered from the effects of malaria a course of about 8 injections of neoarsphenamine (0.6 Gm.) is given. This is followed by a series of 12 bismuth injections. After a rest period of four weeks a course of 12 intravenous injections of tryparsamide in doses varying from 0.5 to 2.5 Gm. is given. Some recommend as many as 40 to 50 injections of tryparsamide. It must be borne in mind that an ophthalmologist keep careful check of the eyes while administering tryparsamide. The Swift-Ellis method of treating neurosyphilis is practiced much less now than formerly. However, the results obtained in treating early neurosyphilis by this method are very excellent provided the technic is carefully carried out. During this entire time, the patient is constantly carefully checked up by physical and laboratory means including ophthalmoscopic and visual-field examinations.

SYPHILIS AND PREGNANCY

It was formerly thought that pregnant women did not tolerate very well antisyphilitic treatment. Consequently many women were carried through a pregnancy on insufficient therapy. If syphilis is discovered early in pregnancy, 15 injections of neoarsphenamine (maximum dose 0.45 Gm.) and 15 injections of bismuth salicylate in oil should be given. If discovered late, treat up to the termination of pregnancy. It is desired that treatment of syphilis in pregnancy should terminate with an arsenical preparation because of its great spirocheticidal properties. Treatment should be continued at the termination

of the pregnancy. A syphilitic woman should receive some treatment with every pregnancy. In this way much can be done to prevent prenatal syphilis. Every pregnant woman should have a Wassermann test early in the pregnancy and repeated at the seventh month of gestation.

PRENATAL SYPHILIS

Prenatal syphilis is preventable. The best treatment is prophylaxis—the discovery of syphilis in the mother before the birth of the child and the institution of continuous treatment up to the termination of the pregnancy. Unfortunately the disease is usually not discovered until it has become generalized. Such syphilis is comparable to acquired syphilis in the secondary stage and requires vigorous treatment for the sake of the child as well as that of the community. In this stage it is very virulent.

The arsphenamines are the drugs of choice. A few experts give neoarsphenamine or arsphenamine intravenously. For the most part, however, neoarsphenamine is employed and it is injected subcutaneously (Cole), or intramuscularly (Rosen). Cole dissolves the drug in 2 to 3 cc. of sterile distilled water and injects it under the loose tissues on the side of the scalp, next to the fascia. Five one-thousandths to 0.01 Gm. per kilogram of body weight is the dose administered. Rosen employs the same doses intramuscularly (buttock). Sulfarsphenamine in doses of 0.02 Gm. per kilogram of body weight is preferred by Moore. The total dose is dissolved in 2 or 3 cc. of sterile distilled water. An injection is given each week up to a total of 8 or 10. The arsenicals are given in alternate courses with an insoluble bismuth preparation (5 mg. per kilo). At least 5 courses of an arsenical and 5 courses of bismuth should be given. Some physicians, especially pediatricians, prefer to use acetarsone (stovarsol).

Good results may be obtained by employing bismarsen alone. Two injections are given weekly in courses of 20 each, with rest periods of two to four weeks between courses. Three to 5 courses are usually sufficient. Some place reliance on bismuth alone. Doses of 5 mg. per kilogram are at first given with a maximum of 100 mg. per kilogram. Children of eight to ten years of age receive half the adult dose. The prepara-

tion preferred is bismuth salicylate in oil and the injections are given intramuscularly (buttock) in courses of 16 each, and with rest periods of four weeks. Iodides are not used as they are poorly tolerated by children. Mercury rubs are sometimes used in place of bismuth. Treatment is continued until the blood and the spinal fluid Wassermann tests have been negative for one year. General care must be of the best and breast feeding must be insisted upon.

For the late prenatal syphilis, much the same system is used as for acquired latent syphilis. Interstitial keratitis and eighth-nerve deafness require energetic treatment with alternating courses of an arsenical and a bismuth preparation. The iodides are very valuable in this stage of the disease. Interstitial keratitis should be treated in conjunction with an ophthalmologist. The local treatment of the eyes is very exacting. In resistant cases, nonspecific therapy is helpful—boiled milk, typhoid-paratyphoid vaccine or even malaria therapy. Little can be done for juvenile tabes or dementia paralytica. These conditions present individual problems.

REACTIONS

The subject of reactions following the administration of antisypilitic remedies is a large one and cannot be discussed here. Care in the preparation and administration of the drug will avoid many Herxheimer and nitritoid reactions. So will careful preparation of the patient. Any deviation from the normal course calls for a restudy of the patient and the conditions under which treatment is being administered. A change of apparatus or even of the drug may be necessary. Finally in order to avoid all untoward reactions, the physician must be constantly mindful of the complications that naturally accompany the treatment of syphilis and must use his best judgment to avoid them.

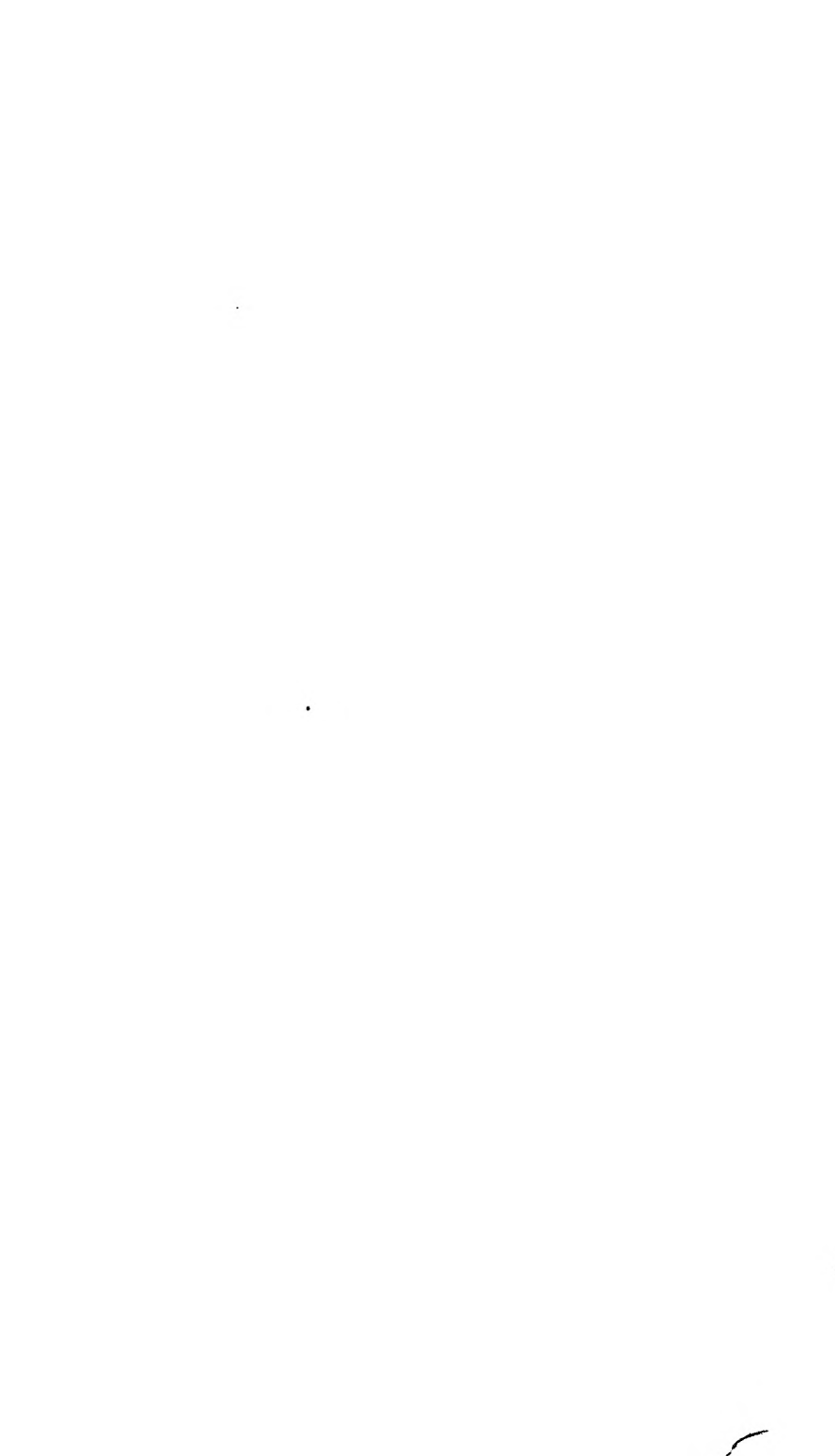
CONCLUSIONS

The best treatment for syphilis is prophylaxis. The campaign against this modern scourge is doing much to educate the lay public. Public health agencies throughout the country are facilitating methods of diagnosis and treatment. The free distribution of drugs to the indigent is making it possible for

large numbers to obtain adequate treatment. The decrease in price of antisyphilitic drugs is helping many to complete their treatment who would otherwise discontinue medication. Routine blood Wassermann tests of every child, every pregnant woman, every man and woman employed and every person that consults his physician for any cause whatsoever and every patient that enters a hospital or clinic for medical or surgical care would reveal many cases of latent syphilis. Their immediate treatment would prevent the more serious complications of late syphilis and would prevent the spreading of the disease. The drive on syphilis is on! Let every physician administer to every syphilitic under his care at least 30 injections of an arsenical and 30 injections of bismuth in continuous alternate courses, provided the patient is young and strong and can tolerate this amount of medication. Syphilis involving special organs requires individual appropriate measures.

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PHYSICAL THERAPY IN DERMATOLOGY, EXCLUSIVE OF x -RAYS AND RADIUM

THIS subject is so extensive that only generalities and indications and descriptions of methods of therapy useful to the general practitioner can be discussed in the space allotted. Very few technical details will be mentioned. Physical therapy is a very important branch of dermal therapeutics but should not be used as a "path of least resistance" and a lazy substitute for the frequently arduous mental labor involved in discovering and removing the cause of a dermatosis, which is the only truly scientific and logical remedy. As MacKee has stressed, the better trained a dermatologist is, the less he relies on physical therapy compared with etiologic and the proper topical or internal therapy.

Ultraviolet Irradiation.—Although ultraviolet irradiation has been advocated for a large number of skin diseases, many of the good results reported are only impressions which have not been verified or are due merely to the spontaneous involution of a self-limited disease. This form of therapy is not used by dermatologists nearly so frequently as most general practitioners believe. In fact, its use is limited to 10 or 12 diseases. In most dermatoses the best results are obtained by solar irradiation or, as this is rarely available, by artificial irradiation which most closely resembles that of the sun. Carbon arc lamps emit an irradiation most like that of the sun but because the required exposures are so long, they are rarely employed by dermatologists although they are useful for home

treatment. Because of the shorter exposures air-cooled quartz lamps are used by most American dermatologists. The cold quartz lamp is especially useful for office work because the greater intensity and proportion of short rays and the small amount of heat involved permits the lamp to be brought close to the body, thereby greatly shortening the time of exposure. This form of irradiation causes more peeling but less severe erythema and pigmentation and no blistering. The results, however, are no better than those obtained with the older types of lamps except perhaps in pityriasis rosea. The lesions of this disease seem to peel much more than the surrounding skin following cold quartz irradiation and usually completely disappear after 4 to 6 biweekly peeling doses. In my experience, ultraviolet irradiation is the only treatment which shortens the duration of this self-limited disease which, if untreated, may persist for one to four months. The objection to the cold quartz lamp is that at times a blistering effect and pigmentation is desired. The cold quartz light because of its low heat can be used also with an applicator in body cavities and in contact with single lesions on the skin. This treatment at times seem to abort the development of early pustules of acne vulgaris and folliculitis and to hasten the healing of patches of impetigo contagiosa.

Although ultraviolet irradiation has some bactericidal action, this is too slight to be of much practical importance. Light therapy is employed for both its general and local effect. The former is obtained by frequent suberythema doses to the entire body and is of distinct benefit in preventing recurrences in disseminated neurodermatitis and psoriasis and, combined with the preliminary application of a crude coal tar ointment, in the Goeckermann treatment of widespread psoriasis. Generalized ultraviolet irradiation also has a useful tonic effect in furunculosis, tuberculosis cutis, Bazin's disease and deep sarcoids. In these diseases the entire body, regardless of the sites of the lesions, should be irradiated. In fact, the same results have been obtained experimentally with generalized irradiation even when the actual lesions have been shielded. Occasionally ultraviolet irradiation may be used to restore pigment in the achromic type of pityriasis versicolor and in secondary depigmentation following psoriasis, syphilis and other

diseases. The application of a photosensitizing substance, such as oil of bergamot, followed by an erythema dose of ultraviolet light has been advocated as a means of restoring the pigment in patches of vitiligo but, in spite of several trials, I have had no success with this method.

Localized ultraviolet irradiation is used in pityriasis rosea, psoriasis, parapsoriasis, the various types of alopecia, acne vulgaris, rosacea, furunculosis, erysipelas, chronic ulcers and wounds, and for the peeling of pitted scars. Several of these conditions are self-limited so that it is difficult to evaluate the effect of therapy, but most investigators now agree that ultraviolet light in very strong doses is one of the best, if not the best, form of treatment for erysipelas. As is well known, sunlight or artificial ultraviolet irradiation usually causes a distinct temporary improvement in acne vulgaris but unfortunately the effect is superficial and seldom permanent. It is less helpful in the erythematous and pustular than in the comedo type and is of very little use, except for its systemic effect when given over the entire body, in the severe forms of acne. Personally, I consider that the use of ultraviolet irradiation in acne vulgaris is indicated only in mild cases, in very young patients, and in those who have not been cured by or refuse roentgen therapy. It should be employed in conjunction with the proper topical and internal remedies and should not be expected to effect a cure per se.

The water-cooled quartz (Kromayer) lamp has the special advantage that it can be used with pressure with a quartz applicator to produce a stimulating or destructive effect on small areas. Large doses have a blistering and dehematizing effect. This lamp is used chiefly for stimulation of the circulation and hair follicles in patches of alopecia areata, on single deep acne pustules and furuncles, and in blistering doses in nevus flammeus ("port-wine mark"), telangiectasia, radiodermatitis, tuberculosis cutis and adenoma sebaceum. The Kromayer lamp with a nickel oxide filter which was devised by Wood, causes fluorescence of hairs infected with fungi but not of normal hairs. This is a very effective means of locating the infected hairs in tinea capitis or sycosis so that these can be removed for microscopic examination and culture. It is used not only in diagnosing a fungus infection but also in following

the results of therapy and in order to determine if a complete cure has been obtained. Various strains of fungi have a characteristic fluorescence both on the hairs and in culture media. Early telangiectasia and pigmentation from roentgen irradiation can frequently be detected with the Wood filter before it is visible in ordinary light.

In spite of the recent widespread fad for ultraviolet irradiation this therapy, which is usually regarded as beneficial and harmless, may produce ill results. One frequently obtains the history of a lupus erythematosus starting after a sunburn and a preexisting lupus erythematosus may be greatly aggravated or become disseminated after exposure to solar or artificial ultraviolet irradiation. Herpes simplex frequently arises from the same cause. In sensitive patients, an urticarial, eczematous or erythema multiforme-like reaction may follow overexposure to sun. These reactions are usually transient but occasionally a persistent erythema known as erythema solare perstans may be seen. A condition known as sailors' or farmers' skin, in which the skin appears prematurely senile, dry, scaly, wrinkled, atrophic and hyperpigmented, occurs in some individuals, especially blonds with delicate skin, after long-continued frequent overexposure to sun. This type of skin is peculiarly susceptible to the development of prickle cell epitheliomas. Pellagra, xeroderma pigmentosum, hydroa aestivale and berlock dermatitis are other dermatoses associated with photosensitivity. Erythema doses of ultraviolet irradiation should never be used on patients with extensive psoriasis, neurodermatitis or oozing eczema as they may produce acute dissemination of the eruption and even, at times, an exfoliative dermatitis with a lethal outcome.

Electrolysis.—This is a useful form of dermatological therapy and should be employed by physicians and not, as is generally the case at present, by untrained laymen. Its use requires the same medical and surgical training and knowledge of antisepsis as is needed for other procedures. The galvanic current is obtained from the negative pole of an ordinary 20-volt dry battery and usually no more than $\frac{1}{2}$ to 1 milliampere of current is used. A platinum needle is attached to the negative pole and a damp sponge, which the patient holds in her hand, to the positive pole. The electrolytic action causes de-

struction of the treated area by a collection of caustic or destructive chemicals around the needle. Electrolysis is used chiefly for hypertrichosis but also for the destruction of hairy and nonhairy, small pigmented nevi, nevi aranei ("spider nevi") and small soft fibromata; and for the obliteration of telangiectatic blood vessels associated with rosacea or radio-dermatitis. In the treatment of hypertrichosis the needle is inserted vertically into the hair follicle and allowed to remain until the hair can be removed without traction. With $\frac{1}{2}$ to 1 milliamperes current this requires from ten to sixty seconds, depending upon the coarseness of the hair. In order to avoid undue irritation of the surrounding tissues and subsequent scarring, it is extremely important that the needle be inserted directly into the follicle and that the insertions are not too close together. In treating a hairy nevus it is advisable first to destroy the hairs as the reaction from this process is usually sufficient to obliterate the nevus. If not, after all the hairs have been removed the remains of the nevus may then be treated. Nonhairy nevi are best treated by multiple horizontal insertions, taking care to keep the point of the needle above the skin surface in order to prevent depressed scars. "Spider nevi" can frequently be destroyed by a single vertical insertion into the central punctum. Telangiectatic vessels can be obliterated by very superficial vertical insertions. The electrolysis causes an obliterative endovasculitis which changes the dilated, hollow, red vessels, filled with blood, into white, solid cords of scar tissue.

In cataphoresis, the same type of current is applied with large electrodes. The application of a negative electrode is supposed to cause vasodilatation and softening of the treated area, while the use of the positive electrode produces the opposite effect. It has been contended that various ions, especially zinc, chlorine and copper, may be introduced into the skin with a galvanic current. In the vascular clinic at the New York Post-Graduate Medical School and Hospital patients with scleroderma, sclerodactylia, Raynaud's disease, and various forms of alopecia have been treated with beta-acetyl-methylcholine by cataphoresis. In many cases, the results have been striking in the first three conditions but this treatment has not been effective in alopecia.

High frequency currents are now used extensively in dermatology and have to a large extent replaced many of the older methods used for destruction of various growths on the skin. These currents produce heat in the tissues. If the heat is sufficient to cause destruction of the tissues, the method is known as surgical diathermy; if it is milder but sufficient for a therapeutic effect, it is known as medical diathermy. This method in general is also called endothermy or in popular parlance, "the electric needle." The advantages of surgical diathermy as compared with other methods are that there is usually much less bleeding because the blood vessels are destroyed in the process, the amount of destruction can be controlled, no sutures are required and the final result is a dry wound which, if small, may not require a dressing. The disadvantages are that healing takes place by secondary intention, forming an irregular scar which is more likely to become keloidal than the thin linear scar following skilful scalpel surgery. Surgical diathermy is often followed by poor results, especially unnecessary scarring, when because of its apparently easy technic it is employed by physicians without adequate skill and experience in this procedure. In using this method it is necessary to attain a "happy medium" between two opposite objectives, namely to completely destroy the lesion, and on the other hand to produce as little scarring as possible. Considerable experience is required to learn the correct depth to which the destruction should reach. With proper technic, large, deep lesions can be removed with surprisingly little resultant scarring. When dealing with malignant lesions, scarring is of secondary importance whereas it is of utmost concern when treating benign lesions for cosmetic reasons. Except for very small superficial growths it is advisable to use a local anesthetic and in all cases the usual antiseptic surgical measures should be followed.

There are three forms of surgical diathermy—electrodesiccation, electrocoagulation and the cutting current ("endotherm knife"). **Electrodesiccation** is the most frequently used. It destroys the tissues by dehydration. This is a monopolar current of 15,000 to 35,000 volts and about 200 milliamperes which is derived from the secondary winding of the high frequency transformer. Its effect is more easily controlled than

that derived from the primary winding and it is possible to obtain a very fine spark which in one or two seconds will destroy a tiny superficial lesion without scarring. The lesion may be destroyed by insertion of the needle or by the spark without actual contact with the needle. This method is used for the destruction of warts, fibromas, senile angiomas, mollusca, granulomata pyogenica, keratoses, basal cell epitheliomas, nevi, nodules of lupus vulgaris, tuberculosis verrucosa cutis, cavernous angiomas and lymphangiomas. In most of these lesions, after the electrodesiccation it is usually desirable to curet off the dehydrated remains of the former lesion and desiccate the base. This procedure makes more certain the complete destruction of the lesion and stops any bleeding, leaving a dry wound. Senile freckles, the so-called "liver spots," and ordinary freckles may be removed without scarring by means of very careful and light electrodesiccation. I have found that even hypertrophic scars following endothermy itself can be flattened down by further electrodesiccation. In a few patients with patches by hypertrophic lichen planus and circumscribed lichenified eczema which resisted roentgen therapy and all other measures, as a last resort, I have used electrodesiccation with very gratifying results.

Large, pigmented, nonhairy nevi can be removed without scarring more quickly if cautious electrodesiccation is used for the first one or two treatments and then followed by electrolysis than if the latter is used from the beginning. Electrodesiccation should not be used for hairy nevi as it is impossible to destroy hairs by this method without causing scarring.

Electrocoagulation is a bipolar current obtained from the primary winding of the high frequency transformer. It has the same oscillations as that which produces electrodesiccation but is of lower voltage (maximum 1500 volts) and higher amperage (1500-6000 milliamperes). It has a much deeper and more destructive effect, which is more difficult to control, than that of electrodesiccation and therefore produces more scarring. In my opinion, its use should be limited to the destruction of large, deep, malignant growths, extensive and verrucous tuberculosis cutis, lymphangiomas, and cavernous hemangiomas in adults, which do not respond to radium. The

amount and extent of the destruction can be controlled by using a bipolar electrode consisting of 2 needles, 2 mm. apart.

The **cutting current** is a current of 500 volts and 5 milliamperes obtained from the primary winding of the high frequency transformer which may flow through an ordinary needle or a wire loop. By means of coagulation of the tissues, this current cuts like a sharp scalpel. There is much less bleeding because the coagulation seals the blood vessels and lymphatics. For this reason, this method has been advocated in preference to scalpel surgery in the removal of malignant growths on account of the supposedly less danger of metastases. Statistics, however, have failed to prove this contention. On the same premise, the cutting current with the wire loop has been used for obtaining biopsy specimens but the specimen thus obtained is often unsuitable for histological examination because of the coagulation of the tissues and it has been shown that specimens obtained without undue trauma by means of a biopsy punch or scalpel do not produce metastases. The cutting current is used chiefly for removal of pedunculated growths, melanomas, and very deep and malignant cancers, especially prickle-cell epitheliomas of the lips, tongue and cheeks. Because of the coagulation necrosis from this method it is impossible to suture the wounds and the subsequent scar may be large and disfiguring. For this reason the endothermy knife should not be used if a good cosmetic result is important.

Medical diathermy is a bipolar current derived also from the primary winding of the high frequency transformer. The amount of current tolerated depends upon the size of the electrodes, the larger the electrode the greater the current. One should start with a current of 200 to 300 milliamperes which may be increased gradually to 3000 milliamperes or more but the dosage should be regulated by the effect on the patient rather than by the reading of the milliampere meter. The duration of the treatment varies from ten to thirty minutes. This method is of very little use in dermatology and is employed chiefly for softening of thickened scars, keloids and scleroderma. Several years ago, medical diathermy was proposed for cases of generalized lichen planus but the results were usually so unsatisfactory that its use for this purpose has been abandoned.

The actual cautery causes marked destruction, which is very difficult to control and produces unsightly scars. It is seldom used by dermatologists except occasionally for warts, keratoses, leukoplakia, etc.

The high frequency Oudin current applied through a vacuum glass tube is occasionally used for its stimulating effect and for the production of localized hyperemia in conditions such as alopecia areata, diffuse alopecia, hypertrophic scars, keloids and in areas with sluggish circulation. Although I have no statistical confirmation, my impression is that this method produces more satisfactory results than ultraviolet irradiation in the various forms of alopecia.

Solid Carbon Dioxide.—Therapeutic refrigeration with solid carbon dioxide gas, which is known as carbon dioxide snow or "dry ice," is still frequently used though not so often as formerly. It is no longer indispensable as newer procedures have been found which give as good or better results in most conditions in which this method was formerly employed. The Cortat-Jacob Cryocautery in which the carbon dioxide gas escapes into various shaped and sized copper cylinders and in which the pressure can be accurately measured in kilograms is the most convenient and accurate form of application. This apparatus is, however, quite expensive and, with experience, equally good results can be obtained from solid carbon dioxide produced by the escape of the gas from a tank into a cylinder made of ordinary blotting paper and adhesive tape or from a piece of "dry ice" from a neighboring drug store or confectionery shop. This method produces its effect through a destructive action on the tissues and, depending upon the strength of the application, causes erythema, vesiculation, necrosis and ulceration. The strength depends upon two factors—the duration of the application and the pressure used. Of these two, the latter is far more important. Although the effect is doubled by doubling the time, it is much more than doubled by doubling the pressure. The amount of pressure and the duration of the application required for any lesion can be learned only by experience and depend on the type, size and thickness of the lesion, the type of the skin and age of the patient, and other factors. The cosmetic result from this treatment is usually very good as the lesion is replaced by a soft, pliable

inconspicuous scar. Solid carbon dioxide is used for the destruction of pigmented and vascular nevi, warts, keratoses, lymphangiomas, nodules of lupus vulgaris and patches of lupus erythematosus. Personally, I use this method only for large, darkly pigmented, verrucous, hairy nevi which are too large and thick to be adequately treated with electrolysis or surgical diathermy and for nevi flammei, very small angiomas, and discoid patches of lupus erythematosus. I consider that radium is the method of choice for cavernous hemangiomas and the so-called "strawberry mark" vascular nevi because it causes no pain, blistering or scaling and less scarring. The method of giving intravenous injections of gold sodium thiosulfate following the local application of solid carbon dioxide to patches of discoid lupus erythematosus is often particularly effective as, because of the local hyperemia produced by the irritation, the drug is apparently concentrated in the patches. Aside from solid carbon dioxide, cold is of little use in dermatology except for freezing patches of larva migrans with an ethyl chloride spray, and cold wet compresses in acute vesicular and bullous dermatitides accompanied by edema and itching, especially on the eyelids.

Heat.—Hot wet dressings are a useful adjuvant in the treatment of furunculosis, sycosis vulgaris and deep cystic or indolent pustules of acne vulgaris. An especially effective form is 1 drachm of Vlemminckx's solution (lotio calcis sulfurata) to 4 ounces of hot water. Dry heat by means of an incandescent electric bulb or an electric pad relieves the pain and hastens the involution of lesions of herpes zoster. Moist or dry heat through the induced hyperemia may accelerate the healing of indolent ulcers.

Constant wet dressings of bland solutions are of great benefit in acute dermatitis and moist eczema and of various antiseptic solutions, in furuncles, carbuncles, paronychias, erysipelas and other pyodermas. Frequent or almost continuous hot soaks of a 1:5000 potassium permanganate solution usually give the best results in acute, oozing, vesicular, secondarily infected dermatophytosis of the feet. In all these conditions the results are due chiefly to the heat and moisture rather than to the particular solution used. Boric acid solution, bichloride of mercury, 1:1000 to 1:5000 solution, metaphen 1:5000 solu-

tion, Burow's solution diluted 1:8 to 1:20 with water or boric acid solution, silver nitrate 1:1000 to 1:5000 solution, potassium permanganate 1:5000 solution, dilute Vlemminckx's solution and wet dressings of magnesium sulfate, are the drugs most frequently used for this purpose.

Balneotherapy.—Medicated baths are not curative but give considerable relief to patients with exudative, itchy and scaly dermatoses. Continuous baths with potassium permanganate 1:2 grains to the bath are frequently used in pemphigus, widespread pyoderma and dermatitis venenata due to poison ivy. Colloid, starch, bran, oatmeal, pine tar, magnesium sulfate, sulfur and sea water are added to the bath for their antipruritic effect. Although bicarbonate of soda is usually a harmless, soothing drug and is frequently used in baths to relieve itching, it occasionally has the opposite effect and in susceptible individuals may produce an erythematous, scaly dermatitis which is frequently more itchy than the original disease. For this reason, its use should be avoided.

Massage.—The use of this modality is limited to the treatment of keloids, hypertrophic scars, scleroderma, and the various forms of alopecia. Long-continued, conscientious massage of areas of scleroderma frequently gives better results than most of the more complicated and spectacular means of treatment which have been proposed for this disease. Massage is best performed using a kneading motion with cocoa butter.

Posture, rest and regulated exercise are of benefit in varicose eczema, ulcers and hemostatic dermatitis. Unna's paste (zinc oxide 10, gelatin 30, glycerin 30 and water 30) or some elastic adhesive bandage gives the necessary support to the weakened vein walls in these conditions.



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CARDINAL POINTS IN THE DIAGNOSIS OF DRUG ERUPTIONS

For a discussion of the cardinal points in the diagnosis of drug eruptions, it is necessary to restate the definition of the term itself, and emphasize the importance of the morphology, time factor, location, distribution, and duration of such lesions together with careful history taking. These and other requirements will be elaborated upon in the following pages.

Definition of Drug Eruption.—An eruption of the skin or the mucosal orifices that appears from the oral or parenteral administration of a medicine may be designated as dermatitis medicamentosa. The eruption that appears as a result and at the site of a local application, may be termed dermatitis venenata. It is not always possible, however, to eliminate the question of the absorption through the skin after the topical application of some remedies, and the internal use of a drug may cause skin lesions at times indistinguishable from those produced by external application. Therefore, the general term of drug eruption is applied to all types of visible lesions produced from the use of drugs, irrespective of the mode of administration.

Frequency of Drug Eruptions.—There are now known about 350,000 organic drugs and a few thousand inorganic chemicals or combinations used as medicines.¹ About 1500 of these are stocked in an average pharmacy.² Any drug of therapeutic value will be likely to produce an eruption or some other undesirable effect, in some individual with an idiosyncrasy to the particular agent. Drugs in millions of prescriptions are

dispensed yearly in private practice, hospitals, clinics, etc., aside from those used as household remedies. Nevertheless the incidence of drug eruptions (following oral or parenteral use) is surprisingly low. They are not mentioned among the 10 ranking skin diseases as is the case with dermatoses due to contact (dermatitis venenata) with various external agents.³ They are presumably nowhere so frequent as eruptions produced by foods.⁴ Sutton⁵ in a recent statistical study of over 100,000 consecutive general admissions to the University of Kansas Hospital and Out-patient Department, found that the ratio of drug eruptions to all other illnesses was 1 to 2000 (0.05 per cent). Sutton's figures, on the frequency of drug eruptions, based on 4000 various dermatological cases observed in private practice showed a proportion of 1 to 310 (0.32 per cent). Of 56,634 admissions at the New York Skin and Cancer Unit of the New York Post-Graduate Hospital, during the last five years, eruptions from drugs occurred in 1 out of 651 patients with various other dermatoses (0.15 per cent).

Morphology. Polymorphism.—A drug eruption may assume almost every known form of skin or mucous membrane lesion, *i. e.*, urticarial, macular, papular, nodular, tumor-like, vesicular, bullous, pustular, furuncular, ulcerative, gangrenous, hypertrophic, atrophic, pigmentary and depigmentary lesions. Occasionally there are no visible manifestations but purely subjective symptoms like itching, burning, formication, alteration in taste, smell, etc.

An extreme variation in the type of drug eruptions may appear in different individuals following the use of the same drug. This polymorphism, as it is called, is one of the cardinal characteristics of drug eruptions and of diagnostic importance. The same type of an eruption may appear in different individuals from the use of different drugs. The same individual may have different types of eruptions from the use of the same drug with various relapses.

Although drug eruptions are usually polymorphous in appearance, a majority are primarily either urticarial or eczematous in nature. Such eruptions show histological changes of the epidermis and corium, indicating an urticarial or eczematous picture with its known variations. This group of drug eruptions are believed to be allergic in nature, *i. e.*, due to the de-

velopment of a specific altered state of the reaction capacity of the body, the drug presumably acting as an antigen or sensitizing agent, the skin manifestation being an expression of an allergic phenomenon.

A smaller group of drug eruptions particularly those of a special nature, viz., argyria, arsenical keratosis, bromoderma, and iododerma, etc., present widely different histological pictures in accordance with their clinical appearance. Deposits of silver in argyria, hyperkeratosis from arsenic, and an inflammatory cellular cutaneous infiltration (neutrophils, eosinophils), in the bromide and iodide eruptions. Such special eruptions not only indicate the drug or group of drugs responsible, but also a different mode of genesis. While an allergic factor plays a rôle in some instances (halogens), they are mostly due to cumulative effects. Another special type of lesion that may indicate the drug or group of drugs responsible, is the so-called "fixed" eruption. This is in reality a recurrent skin eruption in which each relapse is characterized by a flare-up of a former lesion. It generally assumes at its onset an urticarial, erythematous, bullous, or even an eczematous appearance followed by pigmentation. Such drug eruptions are considered of an allergic nature. No longer is it believed that phenolphthalein alone is capable of producing this type of lesion, for according to the reports in the literature quite a few drugs, *i. e.*, acetphenetidin (phenacetin); acriflavine hydrochloride (trypaflavine); antipyrine, aminopyrine (pyramidon) and its compounds; antimony and potassium tartrate; the arsenicals (acetylarsan, arsphenamines, mapharsen, tryparamide); barbiturates; bismuth; cinchophen; iodides; ipecac; ipomea (scammony); isacen; mercury; quinine and the salicylates (aspirin); may also cause the recurrent (fixed) eruption." Not only drugs but physical exertion, psychic stress, alcoholic liquors, foods and autotoxic substances are reported to have caused this peculiar recurrent eruption.

Time Factor.—Cinchonism and salicylism, with a suitable dose or doses of the respective drug, will develop in all individuals without any special susceptibility being required. The metallic pigmentations of the skin will appear in all persons if the use of such preparations is continued over a prolonged period. The urticarial and eczematous type of drug

eruptions however appears only in those who have taken that particular drug on more than one occasion, sometimes for years, without any ill effects. The drug eruption having manifested itself once, it usually reappears thereafter within one to two days after the particular drug is used. Although it is not always easy to prove, drug eruptions of the urticarial or eczematous type appearing presumably with the first dose of the drug, probably are due to a prior exposure of the individual to the particular agent which sensitized him.

It is possible in some instances to determine the interval during which the peculiar change in the reaction capacity of the organism to a drug takes place. This period is about one week, the same time in which serum sickness is apt to develop. This interval during which the development of sensitization occurs is also noted in nirvanol disease, in the case of the sulfanilamide rash and other drug eruptions following the topical application of a drug. Sensitization is more apt to occur with some drugs than others, also when a constant daily dosage leads to a high concentration of the circulating drug. But long after the drug is excreted, a comparatively small dose taken in those previously sensitized, may produce a relapse. Sensitization may develop either from external or internal use of a remedy. Either method of administration thereafter may then produce a recurrence of the drug eruption.

A morbilliform and scarlatiniform generalized erythema, without the usual prodromes of the infectious exanthemata, may appear from the use of various drugs. The sudden onset of such manifestations sometimes with the history of similar attacks is of diagnostic significance. Among the morbilliform and scarlatiniform eruptions is Milian's ninth day erythema. This is reported following the use of various drugs, generally after the arsphenamines and is ascribed by Milian to an activation by the drug of some latent infection present in the system of the affected individual. The ninth day erythemas generally do not recur with the subsequent use of the drug, as is usually the case with most other types of drug eruptions. Their exact pathogenesis needs still further study.

Location.—With the external use of a remedy the eruption that may appear is usually limited to the part to which the agent has been applied. Extension through accidental contact

may take place to other areas of the skin (face, armpits, groins, and perianal region), with intervening normal areas. On the other hand the eruption may become generalized through cutaneous absorption of the drug into the circulation. This is apt to occur with certain drugs like mercury, salicylates, and phenol. Drugs used for inhalation like ephedrine may produce a local dermatitis of the nostrils, face and hands with the subsequent production of a generalized eruption from absorption of the drugs through the nose into the general circulation. Drugs applied to the vagina, rectum, and other orifices, may also produce generalized eruptions in certain instances.

Eruptions from the internal use of drugs are apt to be generalized, involving the face and genitals. Conjunctival and buccal lesions may appear. Photosensitizing drugs (barbiturates, quinine, sulfanilamide, coal tar, etc.), and metallic drugs (silver, gold and bismuth), are more apt to produce eruptions on the exposed parts of the body. Of the metallic pigmentations, that from arsenic is more pronounced on the covered parts. Isolated skin lesions from drugs may appear on any part of the cutaneous surface with no special predilection or at the site of old scars, infections, bites, etc. Generalized eruptions have a tendency to favor the various body flexures and folds.

Arsenic, usually the inorganic form, is known to produce palmar and plantar erythema, hyperhidrosis, and keratosis; bismuth and gold may on occasions produce similar effects; the bromide and iodide eruptions favor the sebaceous areas of the skin; fluorides produce a mottled enamel of the permanent teeth; the use of drugs, causing an extensive exfoliating dermatitis, may cause discoloration and trophic disturbance of the nails.

Duration.—Drug eruptions of the urticarial and erythematous types appear suddenly and often disappear just as quickly provided of course the drug is immediately discontinued. The morbilliform, scarlatiniform and the erythema multiforme-like rashes may last one or more weeks. Spontaneous relapses of eruptions from antipyrine, barbiturates and cinchophen are reported although the drug responsible was not used again. The eczematous type of drug eruption is slower in onset and evolution and may take several months or longer

to disappear. Repeated relapses of the recurrent (fixed) erythematous drug eruption may lead to marked pigmentation, but this will ultimately recede after the responsible drug is discontinued. Bromodermas and iododermas have been known to appear weeks or months after the particular drug had been discontinued and may last for years (granulomatous type).

Establishing the Diagnosis.—The diagnosis of drug eruptions should not be based merely on the history of medication or the presence of the drug in the body fluids and tissues. There is always a possibility for a dermatosis to appear not due to a drug but coincidental with its use. On the other hand patients may deny or forget the use of a household remedy. Some of the foods eaten may have been contaminated, medicated or dyed with some drug or chemical. A remedy may have been used or applied at the various body orifices. Other sources of exposure may have to be investigated, as liquors, cosmetic and toilet preparations. Occupational environment may need to be searched for as the cause of the eruption. Careful, detailed and unbiased history taking is a prime essential in order to establish the true cause and effect.

Cutaneous tests as a routine procedure are at present unreliable in determining whether a drug is responsible for the eruption. Passive transfer experiments in animal or man are in the same category. The administration of a small test dose of the suspected drug is convincing proof, provided a definite relapse of the eruption occurs. Should this fail to appear it does not always rule out the suspected drug as the responsible agent, owing to the desensitization that sometimes develops in certain individuals. If it is not safe to use even a small dose of the suspected drug, then the future avoidance of the particular drug, with the actual use of other drugs taken as a control, should finally determine the one to be responsible. Even with the history of several previous attacks, each time from the use of one particular drug, the elimination of other drugs or causes is advisable, to exclude polysensitiveness. It is surprising how often dermatoses are reported as drug eruptions, based on the single criterion that the patient took a certain drug before the eruption appeared.

General Reactions.—Various gastro-intestinal, neurologic, urinary, or other constitutional symptoms of a mild to severe

degree may precede or accompany the appearance of a drug rash. With skin lesions of a limited distribution or of a mild nature general symptoms are of no consequence. Cutaneous reactions are usually absent in those presenting mental bromism. The reverse is also noted.

Prognosis.—Eruptions from drugs generally fade quickly as soon as the use of the drug is discontinued and eliminated from the body. In those instances where the elimination of the drug is slow, recovery is apt to be delayed. Barring secondary infection or other complications, the urticarial and eczematous drug eruptions disappear without any permanent sequelae. This also applies to the recurrent (fixed) lesions. Bromodermas and iododermas of long standing may leave some scarring after they disappear. With the appearance of purpura after the use of some drugs, the prognosis may be less favorable, owing to the vascular injury induced. In the case of pigmentation from metallic drugs like silver, gold, etc., such pigmentation, once it develops, is apt to remain permanently. The careless use of ergot and its alkaloids may result not only in the loss of an extremity, but also in the death of the patient. The generalized crustaceous exfoliative dermatitis noted from the arsenicals and other heavy metals are a serious complication that may have a lethal outcome. Jaundice from acute yellow atrophy of the liver due to drugs is in the same category.

Congenital Drug Eruptions.—Drug eruptions on occasions appear at birth from the use of some drug by the mother before delivery. It may appear later in the nursing infant provided the breast milk contains the drug being taken by the nursing mother. They have been reported usually with bromides and less so with iodides.

Summary and Conclusions.—The general term of drug eruptions is applied to all types of visible lesions of the skin and mucous membrane produced from the internal or external use of drugs.

The ratio of drug eruptions to all other illnesses is estimated at 1:2000 (0.05 per cent), and to various other skin diseases about 1:651 (0.15 per cent) to 1:310 (0.32 per cent).

Drug eruptions are of polymorphous appearance, *i. e.*, they may assume almost every known form of skin or mucous

to disappear. Repeated relapses of the recurrent (fixed) erythematous drug eruption may lead to marked pigmentation, but this will ultimately recede after the responsible drug is discontinued. Bromodermas and iododermas have been known to appear weeks or months after the particular drug had been discontinued and may last for years (granulomatous type).

Establishing the Diagnosis.—The diagnosis of drug eruptions should not be based merely on the history of medication or the presence of the drug in the body fluids and tissues. There is always a possibility for a dermatosis to appear not due to a drug but coincidental with its use. On the other hand patients may deny or forget the use of a household remedy. Some of the foods eaten may have been contaminated, medicated or dyed with some drug or chemical. A remedy may have been used or applied at the various body orifices. Other sources of exposure may have to be investigated, as liquors, cosmetic and toilet preparations. Occupational environment may need to be searched for as the cause of the eruption. Careful, detailed and unbiased history taking is a prime essential in order to establish the true cause and effect.

Cutaneous tests as a routine procedure are at present unreliable in determining whether a drug is responsible for the eruption. Passive transfer experiments in animal or man are in the same category. The administration of a small test dose of the suspected drug is convincing proof, provided a definite relapse of the eruption occurs. Should this fail to appear it does not always rule out the suspected drug as the responsible agent, owing to the desensitization that sometimes develops in certain individuals. If it is not safe to use even a small dose of the suspected drug, then the future avoidance of the particular drug, with the actual use of other drugs taken as a control, should finally determine the one to be responsible. Even with the history of several previous attacks, each time from the use of one particular drug, the elimination of other drugs or causes is advisable, to exclude polysensitiveness. It is surprising how often dermatoses are reported as drug eruptions, based on the single criterion that the patient took a certain drug before the eruption appeared.

General Reactions.—Various gastro-intestinal, neurologic, urinary, or other constitutional symptoms of a mild to severe

degree may precede or accompany the appearance of a drug rash. With skin lesions of a limited distribution or of a mild nature general symptoms are of no consequence. Cutaneous reactions are usually absent in those presenting mental bromism. The reverse is also noted.

Prognosis.—Eruptions from drugs generally fade quickly as soon as the use of the drug is discontinued and eliminated from the body. In those instances where the elimination of the drug is slow, recovery is apt to be delayed. Barring secondary infection or other complications, the urticarial and eczematous drug eruptions disappear without any permanent sequelae. This also applies to the recurrent (fixed) lesions. Bromodermas and iododermas of long standing may leave some scarring after they disappear. With the appearance of purpura after the use of some drugs, the prognosis may be less favorable, owing to the vascular injury induced. In the case of pigmentation from metallic drugs like silver, gold, etc., such pigmentation, once it develops, is apt to remain permanently. The careless use of ergot and its alkaloids may result not only in the loss of an extremity, but also in the death of the patient. The generalized crustaceous exfoliative dermatitis noted from the arsenicals and other heavy metals are a serious complication that may have a lethal outcome. Jaundice from acute yellow atrophy of the liver due to drugs is in the same category.

Congenital Drug Eruptions.—Drug eruptions on occasions appear at birth from the use of some drug by the mother before delivery. It may appear later in the nursing infant provided the breast milk contains the drug being taken by the nursing mother. They have been reported usually with bromides and less so with iodides.

Summary and Conclusions.—The general term of drug eruptions is applied to all types of visible lesions of the skin and mucous membrane produced from the internal or external use of drugs.

The ratio of drug eruptions to all other illnesses is estimated at 1:2000 (0.05 per cent), and to various other skin diseases about 1:651 (0.15 per cent) to 1:310 (0.32 per cent).

Drug eruptions are of polymorphous appearance, *i. e.*, they may assume almost every known form of skin or mucous

membrane lesion. Occasionally there are no visible signs but subjective symptoms like itching, burning of the skin, alteration in taste, smell, etc.

A majority of the drug eruptions are primarily of the urticarial and eczematous type. These are believed to be of an allergic nature.

A smaller group of drug eruptions assume a special appearance, indicating the drug or group of drugs responsible. As examples may be mentioned ergot (gangrene), arsenic (keratosis), bromides and iodides (granuloma). These are mostly due to cumulative action, selecting various tissues for their toxic effects. Allergic susceptibility may also play some part in these manifestations.

Milian's morbilliform or scarlatiniform erythema of the ninth day is attributed by Milian to an activation of some latent infection by a drug. Such eruptions generally fail to recur with the subsequent use of the responsible agent.

The recurrent (fixed) drug eruption which recurs at the site where the eruption first appeared, is known to follow the use of numerous synthetic organic compounds, also inorganic drugs like mercury and bismuth, and liquors, foods, psychic stress, physical exertion and autotoxic substances.

There is no special location or distribution that characterizes most drug eruptions, when fully developed, from other dermatoses. They are usually generalized, often involving the face and body flexures. Those following the external use appear at first at the site of application.

Careful and tactful history taking is a prime essential for a proper diagnosis. It may be necessary to administer a small test dose of the drug and others that the patient may be taking to determine the cause and effect. This may even be necessary in those with repeated relapses from a certain drug in order to exclude polysensitiveness. Skin tests are generally unreliable as confirmatory evidence.

Drug eruptions as a rule appear suddenly and recede rapidly when the drug is discontinued and eliminated.

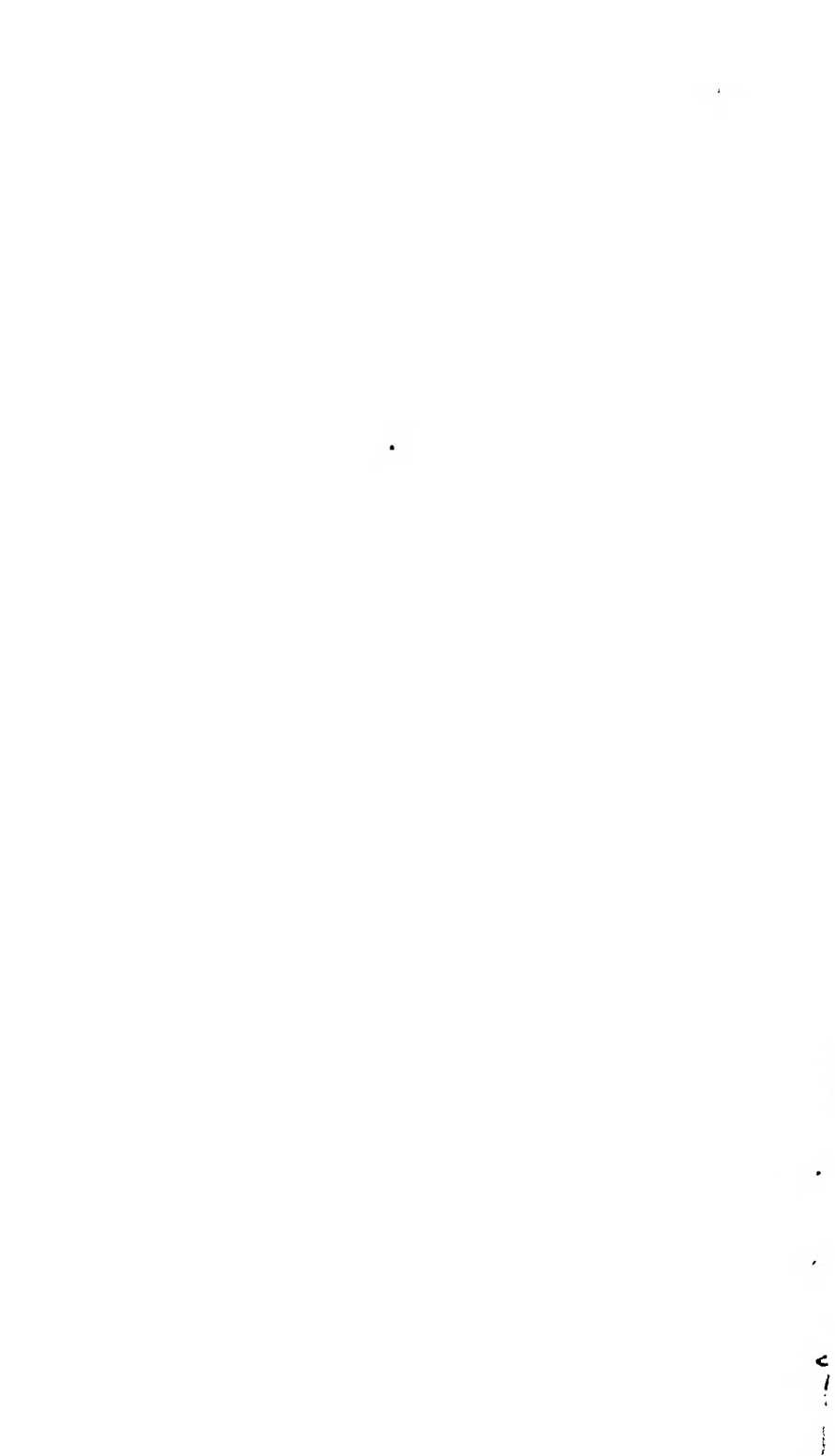
Barring secondary infection or other complications there are no permanent sequelae. Exceptions are the pigmentation from the metallic drugs, keratoses and the scarring following tuberculous bromodermas and iododermas of long standing.

The prognosis of drug eruptions is usually favorable. Exceptions are the crustaceous exfoliative dermatitis, purpura, gangrenous lesions, and jaundice from acute yellow atrophy of the liver.

Drug eruptions may appear at birth or in infants nursing from the breast milk of the mother taking bromides or iodides.

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CLINIC OF DR. SEYMOUR H. SILVERS

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CUTANEOUS TUBERCULOSIS

WHEN the tubercle bacillus invades the skin, certain changes result, which we recognize as the various forms of skin tuberculosis. The gross and histological appearance of the lesions depends on numerous factors. Both general and local immunity and allergy determine the extent, shape, and configuration of the skin eruption. The presence or absence of other foci of visceral tuberculosis, the age of the patient, and to some extent the racial factor, all enter into influencing the clinical picture and the course of skin tuberculosis. Previous exposure to the tubercle bacillus also modifies the subsequent skin infection.

A great deal of controversy has centered about the question of the presence or absence of visceral tuberculosis in cases of skin tuberculosis. The conception that tuberculosis of the skin protects the visceral organs, or at least modifies favorably the course of internal tuberculosis, has been widely discussed and has been accepted by many observers. Wail¹ noted experimentally that guinea-pigs and monkeys in which marked tuberculosis changes occurred in the skin had less severe changes in the internal organs than those animals in which the tuberculosis of the skin was slight or of short duration. Kressner² investigated a large number of patients with skin tuberculosis. She reports that in 91 per cent of papulonecrotic tuberculosis of the skin, in more than 66 per cent of erythema indurativa Bazin and tuberculosis verrucosa cutis, and in more than 58 per cent of scrofuloderma, she was able to demonstrate an internal focus of the disease. In cases of lupus vulgaris, she found 33.7 per cent of inactive visceral tuberculosis and 5 per cent of active visceral lesions. Memmesheimer³

found among 312 patients with lupus vulgaris only 65 with verified pulmonary tuberculosis. Of these, only 15 patients had active pulmonary tuberculosis. At Sea View Hospital, our patients with skin tuberculosis invariably show forms of visceral tuberculosis. While the majority of cases show active foci, a few, especially those with lupus vulgaris, have inactive foci. Thus, a review of the last 10 cases seen in our clinic shows the following:

R. N.	Extensive lupus vulgaris	Productive changes throughout the lungs
L. B.	Extensive lupus vulgaris	Extensive pulmonary pathology with positive sputum
A. K.	Moderate lupus vulgaris	Caseous pneumonic lesions
J. S.	Moderate lupus vulgaris	Bilateral caseous pneumonia
R. K.	Moderate lupus vulgaris	Productive changes in both lungs
M. A.	Scrofuloderma	Caseous pneumonia
A. S.	Tuberculosis verrucosa cutis	Extensive caseous pneumonic lesions
J. L.	Tuberculosis ulcerosa	Extensive caseous pneumonic lesions
E. D.	Lupus vulgaris and scrofuloderma	Tuberculosis of vertebrae and larynx
L. W.	Scrofuloderma	Caseous pneumonic lesions

Thus our cases showed foci of internal tuberculosis, most of them active forms. This is not in agreement with the findings of other observers, but the patient usually admitted to our hospital comes primarily because of visceral tuberculosis.

For the sake of clarity, we describe and name various forms of cutaneous tuberculosis. A very interesting form of tuberculosis of the skin which has been recognized and studied is the primary complex of skin tuberculosis or *tuberculous chancre*. While the majority of these cases are seen in infants and children, an adult occasionally presents this form of tuberculous lesion of the skin. It was seen occasionally following the ritual form of circumcision and the piercing of the ear lobes for ear rings. Holt⁴ gathered a number of cases caused by circumcision. In the adult, the lesions are rare, for this form of tuberculosis presupposes the absence of a previous infection. Cases in adults have been reported by Stokes,⁵ Fidler,⁶ and Michelson,⁷ among others. The characteristic of the lesion is an ^{indurated} ^{and} ^{well} ^{defined} ^{edges}, the base of the ulcer being

covered with moist, red granulations. The surrounding skin is hard and purplish in color. The regional glands are enlarged and may continue to be involved even after the ulcer has healed. Finally, the glands may break down. The lymphatics between the ulcer and the regional glands are very often clearly outlined. The glands show caseation on histologic examination, and the bacillus can be recovered. Very often, instead of healing, the ulcer shows, after a few weeks, typical lupus vulgaris structure, both clinically and histologically. The



Fig. 139.—Tuberculosis verrucosa cutis of second and fifth knuckles of the left hand.

tuberculin test, which was negative at the beginning of the ulceration, becomes positive.

Another form of localized skin tuberculosis is *tuberculosis verrucosa cutis*. This is a local infection caused by direct inoculation with the tubercle bacillus, which produces a very mild local reaction. It is seen among patients in tuberculosis hospitals, attendants, physicians, pathologists, and occasionally in butchers. The lesions appear mostly on the exposed parts of the body, run a very chronic course, and give few subjective symptoms. They form hyperkeratotic patches resembling warts on a purplish red base with little induration.

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covered with moist, red granulations. The surrounding skin is hard and purplish in color. The regional glands are enlarged and may continue to be involved even after the ulcer has healed. Finally, the glands may break down. The lymphatics between the ulcer and the regional glands are very often clearly outlined. The glands show caseation on histologic examination, and the bacillus can be recovered. Very often, instead of healing, the ulcer shows, after a few weeks, typical lupus vulgaris structure, both clinically and histologically. The



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The eruption extends peripherally and heals in the center, leaving a fine, thin scar. If left untreated, the lesions may involve large portions of the skin. Therapy is successful if one destroys the surrounding tissue about $\frac{1}{2}$ cm. beyond the border. The actual cautery or the endothermy current may be employed. These are preferable to chemical cautery, for they can be better controlled.

Other clinical forms of cutaneous tuberculosis are *lupus vulgaris*, *scrofuloderma*, *tuberculous ulcerations*, and *generalized miliary tuberculosis*. In these clinical forms, certain criteria must be satisfied for the designation of the tuberculous etiology. The most important criteria are the finding of the tubercle bacillus in the lesion, the positive guinea-pig inoculations, and a focal flare-up after the intradermal injection of tuberculin. Less important factors in the diagnosis of tuberculosis of the skin are the histological studies, the clinical aspect of the lesions, and the coexistence of tuberculosis of other organs.

Because all the criteria could not be satisfied in some forms of skin tuberculosis, Darier⁸ suggested that certain forms of cutaneous lesions be named *tuberculids*. The tuberculids were once considered to be due to the toxins of the tubercle bacillus, but are now regarded as forms of cutaneous tuberculosis. It is difficult in these cases to satisfy all the criteria enumerated above, for very seldom are we able to demonstrate the bacilli in the lesions and very infrequently do we obtain a positive guinea-pig inoculation. This group includes *lichen scrofulosorum*, *papulonecrotic tuberculosis*, and *erythema indurativa Bazin*, which show certain common characteristics. Their prognosis is invariably good, they are more generalized than the other forms of cutaneous tuberculosis, and they give a strongly positive reaction to tuberculin in high dilutions.

Sarcoids are usually classified with the tuberculids. The inclusion of all forms of sarcoids with skin tuberculosis has been questioned lately, for we encounter sarcoid-like lesions in leprosy and in syphilis. The finding on roentgen examination of cystic-like lesions in the bones and marble-like shadows in the lungs has thrown further doubt on the advisability of including all cases of sarcoids, especially those of the Boeck type, with tuberculosis of the skin. The deep type of sarcoid

described by Darier and Roussy is considered a variety of non-ulcerative, erythema indurativa type of tuberculosis of the skin. The tuberculin reaction is of great interest in the sarcoids. The reaction is either entirely absent or greatly diminished. This altered reaction is of diagnostic significance.

There are a great number of dermatoses in which the etiologic factor has not been determined. Some of these dermatoses have been classified from time to time with the tuberculids, suggesting that they were forms of skin tuberculosis. That the skin may undergo nonspecific and secondary changes in a body invaded by the tubercle bacillus cannot be denied. We may find among tuberculosis patients dryness and follicular hyperkeratosis, marked seborrheic and other forms of eczema, pustular folliculitis of the back in bedridden patients, and occasionally amyloid degeneration of the skin. Very common among hospitalized tuberculous patients is pityriasis versicolor, probably due to excessive sweating and contact among patients. These skin conditions are due to poor nutrition of the skin, poor hygiene, emaciation, and degenerative changes in the skin.

Erythema nodosum is very often associated with a positive tuberculin reaction in children and has, therefore, also been classified by pediatricians as a possible tuberculid. We feel that the tuberculous nature of erythema nodosum has not been established and agree with Forman⁹ and others that the disease may be associated with diverse etiologic factors, such as throat infections seen most often in adults. In children, there may be evidence of tuberculous infection.

Granuloma annulare and *lichen nitidus* are other examples of dermatoses of unknown etiology which have been occasionally classified with the tuberculids.

Lupus erythematosus has been so often classified among the tuberculids that its tuberculous etiology has been accepted by many as almost established. Especially is this viewpoint prevalent in continental Europe. The frequency with which tuberculosis of the viscera is found in patients with lupus erythematosus in France has convinced Nicolas and Gaté¹⁰ that tuberculosis is the most likely factor in this disease. This view has not been accepted in this country. In our experience at Sea View Hospital for the past six years, we have seen only 3 cases of lupus erythematosus, one of which was in an em-

ployee of the hospital. This shows a very low incidence of the disease in a hospital which has more than 1600 patients with tuberculosis of one form or another.

The most benign form of skin tuberculosis is *lichen scrofulosorum* (tuberculosis lichenoides), grouped with the tuberculids. It is most common among children. The appearance of the lesions is sudden and may follow an upper respiratory infection or any similar mild disturbance. The eruption is generalized, consists of pinhead- to lentil-sized follicular papules with shiny, scaly tops, yellowish-red rather than bright red in color. These papules usually appear in groups or patches and are best seen on the abdomen or on the back. The tuberculin reaction is usually positive in high dilutions. Histologic studies only occasionally reveal typical tuberculous structures. The prognosis is good. The eruption disappears within six to eight weeks. This is the only type of tuberculosis of the skin which heals without leaving scars.

Papulonecrotic tuberculosis, another of the tuberculids, is also seen most frequently in children and young adults. These lesions have a tendency to appear on the extensor surfaces of the extremities. They are lentil- to pea-sized and develop necrotic centers surrounded by a red border. The prognosis is good. The lesions heal, leaving a fine scar which may be either hyperpigmented or hypopigmented. The histologic structure shows tuberculous tissue changes. Folliculitis and acnitis, and probably the rosacea-like tuberculid of Lewandowsky are aberrant forms of papulonecrotic tuberculosis.

Another tuberculid, *tuberculosis indurativa Bazin*, usually appears on the calves of young adults, mainly females. Other parts of the body are, however, not exempt. It consists of a deep-seated nodule, marble-sized or larger, red, fairly tender, which eventually ulcerates and runs a chronic course. Darier-Roussy sarcoid is also deep-seated, but shows no tendency to break down. The prognosis is good. Sunlight treatment or a suitable substitute gives good results. The lesions heal, leaving scars which may later break down again. The histologic structure is that of tuberculous tissue.

Tuberculosis ulcerosa is usually seen in advanced cases of visceral tuberculosis and is located in the oral cavity or ano-rectal area. It is also called orificial tuberculosis. The ulcers

are flat and very painful. The base is covered with a grayish mass of débris and the border is red and undermined. The organism can be seen on direct smears. Treatment with sunlight and occasionally with grenz rays may be helpful. The prognosis, however, is poor.

Scrofuloderma (tuberculosis colliquativa) was formerly much more common than at present. The glands of the neck



Fig. 140.—Isolated flat patch of lupus vulgaris resembling psoriasis of seven years' duration. Patient has caseous pneumonic lesions.

are most frequently involved. The skin surrounding the sinus is reddish-blue, edematous, and the edges of the broken-down skin are irregular and ragged. The lesion is usually deep and infiltrated, for the underlying bone or gland structure is infected with the tubercle bacillus. The organisms may be seen on direct smears. The guinea-pig inoculation is positive and the histologic studies show typical tuberculous structure. The prognosis is good. Roentgen therapy, sunlight, cod liver oil,

and proper food and hygiene are important in the therapy of this form of tuberculosis. Most of the patients are young, and special care should be taken to prevent the formation of unsightly scars.

Lupus vulgaris is by far the most important form of skin tuberculosis which we encounter. In 1884, two years after the discovery of the tubercle bacillus, Koch demonstrated the organism in lupus vulgaris. Various clinical forms of lupus vulgaris have been described, such as lupus tumidus, lupus ser-



g. 141.—Extensive lupus vulgaris of the buttocks. This patient also showed similar lesions of the scalp, arms, chest, and abdomen.

ginosus, lupus sclerosus, lupus mutilans, etc. These describe the extent, shape, or form of lupus vulgaris in a particular clinical case. In all these forms, however, we must find the typical lupus vulgaris nodule, aptly described as resembling apple-jelly in consistency and color. It is yellowish-red, pinhead to lentil in size, seems solid, but yields to pressure, and ulcerates along the periphery. The center breaks down, ulcerates, may become crusted, and is finally replaced by scar tissue. Lupus vulgaris is a mutilating disease. It destroys the skin. The skin is replaced by a scar, and very often, a prickle-

celled epithelioma develops in the scar. Only recently, such a case came to our attention. A young colored female was discharged from Sea View Hospital in the early part of 1936, after prolonged and fairly successful treatment for lupus vulgaris of the face. The soft part of the nose, part of the upper lip and sides of the face were replaced by smooth scar tissue. She returned to the hospital eighteen months later, showing the complete destruction of the skin of the face and erosion of the underlying bony structures. This began with a small papule in the scar tissue and rapidly involved the entire face. She



Fig. 142.—Lupus vulgaris tumidus in a patient with a scrofuloderma of the neck and tuberculosis of the larynx.

died from the carcinoma which developed in the scar tissue and secondary infection.

Any part of the body may be the site of lupus vulgaris lesions, but the face is the most common area of attack. The explanation for the selection of this area by this mutilating disease has not been adequately given. Trauma, among other reasons, has been offered as an explanation for the face lesion. It is possible that the follicular-sebaceous apparatus, present so extensively on the face, loses its ability to act as a barrier against the tubercle bacillus. Very often, we see the first lupus vulgaris nodule appearing at the ala nasi, an area extremely rich in follicular-sebaceous structures. Men and women are

equally subject to this disease. Both children and the aged are its victims, though as a rule, the first attack is observed during the second or third decade. One of our patients with lupus vulgaris of the face was an elderly Swedish cook, well over sixty years of age, whose attack began in the declining years of her life.

The clinical course of cutaneous tuberculosis, especially that of lupus vulgaris, may be illustrated by short histories of some of our cases from Sea View Hospital.

Case I.—E. D., a colored male, complained of a sore throat, hoarseness, and enlarged cervical glands at the age of sixteen. The glands broke down and discharged pus. A diagnosis of tuberculosis of the glands was made. One year later, a sore developed on the tip of the nose, which in the following two years spread to involve the entire lower nasal area. A similar area also developed under the lower left eyelid. Five years after the onset, the patient showed ragged and puckered scars on the sides of the neck, a crusted, ulcerated lesion of the nose, upper lip and adjacent skin, and a soft marble-sized lesion under the lower left eyelid. Upon repeated physical examination and roentgenograms, the lungs showed no tuberculous infection. The sputum examinations were also negative for the tubercle bacillus. The Wassermann and Kahn tests were negative. A roentgenogram of the larynx and upper spine showed a retropharyngeal cold abscess with a carious focus in the third cervical vertebra. Histologic examinations of tissue taken from the nose, pharynx, and larynx showed tuberculous structure.

The tuberculin reaction was strongly positive in a 1:1,000,000 dilution. While under observation, the patient developed a generalized eruption. On the extensor surfaces of the extremities, the eruption was of lentil- to pea-sized dark-red lesions which developed necrotic centers. On the shoulders, chest, and abdomen, he showed a fine follicular, papular, erythematous, somewhat scaly and grouped eruption. This generalized eruption, diagnosed as lichen scrofulosorum and papulonecrotic tuberculosis, developed following a temperature elevation of 1° to 3° F. which lasted two days. Within eight to ten weeks, both types of eruption had completely cleared, except for some fine scars left on the extremities. This patient, while under observation, showed various forms of skin tuberculosis: scrofuloderma of the neck and under the left eye, lupus vulgaris tumidus of the nose, lichen scrofulosorum, and papulonecrotic tuberculosis.

Case II.—L. B., a single white female, aged twenty-three years, dated her chest disease from the age of seven. She also gave a history of an operation on the right shoulder which she underwent at the age of sixteen. Four years ago, she showed a positive sputum for the tubercle bacillus and pulmonary involvement. At the same time, a skin lesion appeared on the shoulder, which was diagnosed as lupus vulgaris. An attempt was made to excise this lesion. This was followed within a very short time by a generalized eruption of the skin of typical lupus vulgaris nodules. For the past three years, both the pulmonary and skin tuberculosis have been treated conservatively with good

results. The sputum has been negative for the past two years. The skin lesions have slowly involuted under ultraviolet therapy, although even at present, some typical lesions can still be found. Roentgenograms of the right shoulder showed partial destruction of the head, neck, and adjacent portion of the humerus. The glenoid fossa was irregular and jagged. Complete laboratory examination of the blood and urine were negative. The tuberculin test was positive to a 1:10,000,000 dilution. This patient had active pulmonary and osseous tuberculosis and disseminated lupus vulgaris of the skin.

Case III.—R. N., a white male, entered Sea View Hospital at the age of thirty-one years, with a generalized lupus vulgaris involving the scalp, chest, and posterior half of the trunk. Eighteen years before, a small raised area appeared on the buttocks. This was then excised and diagnosed as lupus vulgaris. For the past eight years, the eruption has slowly spread to involve about 15 to 20 per cent of the patient's total skin area. The chest examination showed productive changes throughout both lungs. Laboratory examination of the blood and urine were negative. The Wassermann and Kahn tests were negative. The sputum examination was always negative for bacilli. The tuberculin test was positive to a 1:100,000 dilution. This patient showed an extensive lupus vulgaris with mild pulmonary involvement.

We have found at Sea View Hospital that the best results in treating cutaneous tuberculosis were obtained with conservative methods and that treatment must be individualized. Roentgen therapy gives the best results in cervical adenitis, before the glands have broken down or become soft. When open lesions are present, ultraviolet radiation gives good results. Both the air-cooled and water-cooled forms of ultraviolet therapy are very helpful in lupus vulgaris, erythema indurativa, the various forms of scrofuloderma, as well as the more generalized forms of tuberculosis of the skin. Unfortunately, our personal experience did not include Finsen lamp therapy. Among salves used locally, we recommend highly a 10 to 15 per cent ointment of pyrogallic acid. Adequate food, fairly large doses of cod liver oil, rest, both mental and physical, are very important adjuncts in the therapeutic scheme. Excision of a lesion in lupus vulgaris, whether with the cautery, endothermy knife, or scalpel should be done only when the patient's general resistance is good, in order to prevent a hematogenous or localized dissemination. Occasionally, even ultraviolet radiation may stir up a reaction and dissemination, if given in too large doses in the beginning. It is best to start with suberythema doses, but to give them at one-day intervals and gradually to increase this as the patient's tolerance in-

creases. Intravenous gold therapy has not been helpful in our experience.

Summary and Conclusions.—Our present conception of cutaneous tuberculosis is that the tubercle bacillus is deposited in the skin, either by the hematogenous route, from a contiguous lesion, which stirs up a reaction resulting in one of the various forms of eruptions, or an outside source.

The tuberculids are true forms of skin tuberculosis, although they do not satisfy all the criteria. Unfortunately, there are a great number of dermatoses of unknown etiology which from time to time have been regarded as tuberculids, but whose tuberculous etiology has not been sufficiently established to be accepted in this classification.

We have found that most of our patients with cutaneous tuberculosis also presented various phases of visceral tuberculosis. This may be accounted for by the fact that this hospital admitted the patient primarily for his internal tuberculosis.

The best results in treating the patient were obtained by using conservative measures, ultraviolet therapy, and raising the patient's general resistance.

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PEMPHIGUS

Definition.—Pemphigus (from the Greek *πεμφιξ*, blister) is a disease of unknown etiology characterized by the appearance of blisters or bullae on the skin, usually without any antecedent lesions. The disease is generally fatal.

Varieties.—Four forms of the disease are now recognized: pemphigus acutus, pemphigus vulgaris, pemphigus vegetans, and pemphigus foliaceus. Pemphigus neonatorum is a bullous impetigo due to bacteria, usually pyogenic cocci, and is not to be confused with the disease discussed in this paper.

Incidence.—The disease is infrequently encountered. Statistics compiled by Pollitzer¹ in America over the period 1898 to 1911 show an incidence of 1 case of pemphigus vulgaris per 1500, and 1 case of pemphigus vegetans per 20,000 of all cases of skin disease. Pemphigus acutus and pemphigus foliaceus are even rarer diseases.

Age, Sex, and Race Incidence.—The disease occurs more commonly in persons above the age of forty, approximately equally in both sexes. The youngest individual observed with pemphigus at the New York Hospital during the past five years was twenty-eight. About 60 per cent of the cases in New York occur in Jews, particularly those born in Central and Southern Europe. Cases are met with also in the colored race.

Pemphigus Acutus.—This is the rarest of the varieties of pemphigus. The clinical picture appears to be that of an acute infection which usually terminates fatally within a few weeks during which the temperature is considerably elevated. The diagnosis is made by the appearance at the onset of the

disease of the characteristic bullae which are distributed generally over the body and buccal and perineal mucosae.

Pemphigus acutus has been seen to occur (a) following septic injuries, especially among butchers, giving rise to the term, "butchers' pemphigus"; and (b) following vaccination with calf lymph for the prevention of smallpox.

Pernet and Bullock² isolated an organism from cases of butchers' pemphigus which they believed was associated with the disease. It was a gram-positive diplococcus morphologically similar to but slightly larger than the gonococcus. Subcutaneous inoculation into guinea-pigs of the bullous fluid produced no lesions but when a culture of the organism in broth was inoculated into the pleural cavity, the animals died with a bronchopneumonia in one week. Similar organisms isolated from these bronchopneumonial patches, inoculated subcutaneously, killed guinea-pigs in seven days. Pernet and Bullock did not regard the organism as a skin contaminant because they were unable to refer it to any of the species known to be normal inhabitants of the skin.

Illustration of pemphigus acutus following vaccination was given by Mook³ who reported 6 cases of "pemphigoid dermatitis following vaccination." No etiological agent was found. The laboratory investigations included subcutaneous and intravenous inoculation of bullous fluid into rabbits and guinea-pigs, intravenous inoculation of citrated blood into rabbits, subcutaneous inoculation of citrated blood into guinea-pigs, subcutaneous inoculation of bullous fluid into monkeys. None of the inoculated animals became ill. Foot and mouth disease was sought with negative results by inoculation of bullous fluid into tongue, gums, and lips and also under the skin and around the hoofs of the fore feet of a calf. Blood cultures were sterile under aerobic and anaerobic conditions and cultures of bullous fluid showed either no growth or *Staphylococcus albus*.

Pemphigus Vulgaris.—This is the commonest form of the disease. It may begin on the skin or in the mouth or upon the mucosal surfaces of the external genitalia or anal region. Cases which begin in the mouth are usually of worse prognosis than those which begin elsewhere. Such cases sometimes follow a tonsillectomy or the removal of teeth. The moisture of mucosal surfaces leads to rapid rupture of the bullae which, in

these situations, are represented by areas of whitish, necrotic mucosa or by shallow ulcerations. It is impossible to diagnose the disease if the lesions are confined to the mucosae. After a period which is usually measured in weeks or months, the characteristic bullae appear on the skin thereby enabling the diagnosis of pemphigus vulgaris to be made. In most instances the clinical condition of the patient deteriorates steadily after the appearance of cutaneous bullae which, at first, tend to have a symmetrical distribution. As the disease progresses an increasing area of the skin is involved until the greater portion of the surface is covered with lesions in different stages of development. The earliest stage is a tense bulla which may be little more than a pinhead size vesicle or a bulla whose dimensions are measured in inches. Classically these lesions arise from nonerythematous, normal-appearing skin. The bullae rupture readily with slight trauma and the collapsed roof, contents, and base together form a dry crust which is easily removed. Owing to the superficial situation of the bulla little scarring follows when such crusts fall off. The previous site of a bulla can sometimes be identified by a little hyperpigmentation.

With the onset of the cutaneous lesions the patient often begins to show signs of toxicity, such as anorexia, pallor, weakness, and sometimes elevation of temperature. In the later stages of the disease successive crops of bullae arise in rapid succession and differ slightly in their appearance from those found earlier in that they are less tense and frequently arise from a definitely erythematous area. At this point a remittent fever is present, the mucosal and cutaneous lesions may be very painful, and the general manifestations have increased in severity. Owing to the state of the mouth and lips it is impossible to administer adequate nourishment orally. Finally, the patient, overwhelmed by toxemia, loses consciousness and dies within a few days. The duration of the disease is seldom more than two years and may be considerably less.

Not all patients follow a steady downhill course. Remissions occur and may do so from a state in which survival appears impossible. In practically all cases, the remission is sooner or later followed by a relapse and several remission-relapse cycles may occur until the patient dies of the disease.

It will be convenient, at this point, to consider 3 aspects of pemphigus vulgaris which lend themselves to experimental studies: the bulla, the blood picture, and the cause of the disease.

The Bulla.—The pemphigus bulla arises either intra-epidermally or between the epidermis and corium by seepage of the elements of the blood plasma into these situations. It contains fibrinogen and the fluid therefore clots readily on withdrawal. The bullous fluid usually contains white blood cells whose numbers vary considerably in different bullae. In some, the cell content is so high that a heavy layer is visible through the thin roof; in others the aspirated fluid shows only a slight turbidity. The freshly developed bulla has contents which are bacteriologically sterile; with age, organisms enter the bulla and are predominantly staphylococci and streptococci. The bacteriologically sterile bullous fluid is, as a rule, less turbid than its contaminated fellow and shows a very high proportion—often over 90 per cent—of eosinophils in its cell content. In bullae infected with pyogenic organisms polymorphonuclear leukocytes predominate.

The Blood Picture.—Very little information is available upon the changes in the blood picture presented by the same patient during the progress of pemphigus vulgaris. Unpublished studies of the author upon this subject at the New York Hospital show that there is usually a secondary anemia of moderate degree and an elevation of the total white count. As the patient deteriorates the total white count rises to a maximum which may be as high as 30,000 to 40,000 cells per cubic millimeter, a few days before death. In the last forty-eight hours there is a rapid fall in the total number of leukocytes. The differential white cell count has two constant features: (a) little or no elevation of the total polymorphonuclear count, and (b) a considerable increase in the proportion of immature polymorphonuclears with a corresponding reduction in the proportion of adult polymorphonuclears with the deterioration of the patient. Eosinophilia of moderate degree probably occurs in the early stages of most cases and generally disappears as the disease progresses. In one individual who died after a short stormy course, a high monocyte count was present throughout.

The lymphocyte and basophile counts appear to be little affected.

The Cause of Pemphigus Vulgaris.—Experimental dermatologists are inclined to believe that pemphigus vulgaris is caused by a virus. Evidence for this belief is as follows: (a) certain aspects of the disease, particularly in the severe cases, resemble those produced by infectious agents; (b) no unequivocal visible organism has thus far been demonstrated in studies of blood, bullous and spinal fluids and tissues; (c) the symmetrical distribution of the trophic-like lesions coupled with the relatively common degenerative and low-grade inflammatory changes in the central nervous system suggest a possible neurotropic virus origin of the disease. Urbach claims to have obtained a virus from cases of pemphigus vulgaris, but the relation of his virus to that of herpes has not yet been satisfactorily determined. Carol⁴ has summarized the work of Urbach and other earlier investigators in this field and has recorded his own results following intracerebral inoculation of pemphigus material into rabbits, guinea-pigs and mice. He concluded that a specific virus of pemphigus could not be demonstrated by methods hitherto employed.

The author and F. H. Suskind⁵ felt that there would be greater likelihood of success if the resistance of the experimental animal were lowered before inoculation by generalized irradiation with a relatively heavy dose of x-ray. Using this method, 3 strains of a virus transmissible to mice by intracerebral inoculation and capable of successive passage have been obtained during a study of bacteriologically sterile bullous and spinal fluids from 3 cases of pemphigus vulgaris. One of these strains has been carried on for 85 subpassages in mice and investigation is proceeding of its properties and relation to pemphigus vulgaris. The author is of the opinion that the disease is due to a virus, but the pathogenesis of the disease is still obscure.

The Diagnosis of Pemphigus Vulgaris.—Diagnosis is made by the clinical characters of the disease. There is, as yet, no satisfactory laboratory test. The phytopharmacologic test of Pels and Macht⁶ in which it is claimed that the rate of growth of a certain seedling, *Lupinus albus*, is retarded on an average to a greater extent in the presence of the blood serum of

pemphigus patients than with normal serum, is of doubtful value.

Differential Diagnosis.—It is believed that certain severe cases of erythema multiforme bullosum are identical clinically with pemphigus vulgaris. Differentiation from dermatitis herpetiformis presents less difficulty and is based upon the pruritus, the grouping of the lesions (which are multiform with predominance of vesicles), and the chronicity of dermatitis herpetiformis. Little difficulty should be experienced in differentiating pemphigus vulgaris from other diseases with bullous manifestations, viz., leprosy, syphilis, pemphigus neonatorum, hydroa aestivale, herpes simplex, herpes zoster, epidermolysis bullosa, and pellagra.

Treatment of Pemphigus Vulgaris.—There is no satisfactory treatment of pemphigus vulgaris or of any other variety of pemphigus. As constitutional symptoms occur sooner or later in most cases of the disease the resistance of the patient must be maintained at as high a level as possible. A high-calorie, high-vitamin diet is employed and is well supplemented by the use of iron compounds and liver. The physical nature of the diet must be adapted to the state of the lips, tongue, and mouth. In all stages of the disease, as long as the physical condition of the patient allows, bullae should be opened and dressed with equal parts of olive oil and lime water, or either zinc oxide or boric acid ointments. Crusts should be removed with warm olive oil and the base dressed with the same medicaments as the opened bulla. Mouth washes of a nonirritating fluid containing 1 to 2 per cent of benzocaine are especially indicated in involvement of the buccal and lingual mucosae. Borated talcum dusting powder is helpful especially in the intertriginous areas. As the disease progresses the patient must be placed in bed, preferably with an air or water mattress. The sheets should be well powdered and frequently smoothed to minimize irritation of the easily traumatized skin. Bed sores are liable to form unless the usual precautions are taken to avoid their occurrence. The lower limbs of patients who remain in bed for a long period must be guarded against the development of contractures by the application of removable plaster casts. As the discharge from the cutaneous lesions is often profuse it is desirable to have pajamas and bed clothes

as little in contact as possible with the patient. This can be well attained in some cases by keeping the patient naked save for shoulder and arm coverings and supporting the bed clothes upon a cradle carrying a battery of lamps for warmth. Baths, once or twice daily, of 1:10,000 potassium permanganate should be continued as long as the strength of the patient allows. Sedatives are necessary in cases in which pain is a marked feature and are best administered in the form of phenobarbital, codeine, and ultimately morphine.

Other therapeutic measures of doubtful value include the use of certain drugs, vaccines, and colonic irrigations. Arsenic is the most commonly used drug in the form of salvarsan, sodium arsenate, tryparsamide, and iron cacodylate. Intravenous injections of germanin, a nonmetallic preparation, have recently been employed. Quinine by the intravenous and coagulen by the intramuscular route have also been recommended. Salicin is one of the few oral remedies used. Many different stock and autogenous vaccines (the latter prepared from the throat, the bullae, or the stool) have been tried. High colonic irrigation, using as much as 8 gallons at a time, has had its adherents.

Pemphigus Vegetans and Pemphigus Foliaceus.—The essential difference between these diseases and pemphigus vulgaris is in the development of the cutaneous lesion after the formation of the bulla.

Pemphigus Vegetans.—The bulla rapidly becomes infected with organisms—most bullae have purulent contents when first observed in this disease—soon ruptures and proliferation of the tissues of the base occurs. This results in a papillary scaly lesion in which the epidermis is hyperkeratotic and considerably thickened, sending down long, narrow, projecting processes into the corium. On the vulva the macerating effect of the local secretions upon the lesions produces a strong resemblance to condylomata lata, causing the disease to be mistaken for syphilis. The vegetating lesions are best observed in the axillae, groins, and vulva but also occur on any part of the skin. Secretions from the lesions have an extremely fetid odor.

Pemphigus vegetans must be differentiated from impetigo herpetiformis. The latter occurs during pregnancy and shows

a number of small pustules grouped on inflammatory bases and arranged in a circinate manner.

Pemphigus Foliaceus.—The initial bullae appear over large areas of the skin and produce a condition very similar to a generalized exfoliative dermatitis. Recognizable bullae are not formed after this stage is reached. Considerable scaling results from the casting off of epidermis surmounting the bullae which now have scanty fluid content.

The condition may be mistaken for generalized exfoliative dermatitis in which, however, bulla formation does not occur.

The course, prognosis, and treatment of pemphigus vegetans and pemphigus foliaceus is the same as that of pemphigus vulgaris.

The search for the etiological agent of pemphigus vulgaris during the past few years by the use of methods developed in the study of viruses has quickened interest in the disease. Should pemphigus be shown to be due to a virus the way may be opened to an understanding of the relation between pemphigus and other bullous diseases, such as dermatitis herpetiformis, erythema multiforme bullosum, and the Senear-Usher type of pemphigus, whose etiological agents are still unknown. Although pemphigus is a comparatively rare disease, it is a good starting point for the application of modern exact laboratory procedures to the study of skin diseases in that uncontaminated pathologic material is readily available and the severity of the disease necessitates hospitalization of most cases with, therefore, ample opportunity for close observation. The search for the etiological agent of pemphigus is of more than academic interest as it is now certain that the present empirical therapeutic methods have little influence upon the cause of the disease. The successful management of pemphigus will be brought nearer by knowledge of its cause.

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CLINIC OF DRS. GEORGE W. CALDWELL AND
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THE CUTANEOUS MANIFESTATIONS OF THE ACUTE
EXANTHEMATOUS DISEASES

THE diagnosis of the acute exanthematous diseases depends largely upon a thorough knowledge of the character of the eruptions in conjunction with other clinical symptoms. We have, therefore, limited our discussion to this phase of the subject.

SMALLPOX

(Variola)

Definition.—Smallpox is an acute, contagious disease characterized by a prodromal period of about three days consisting of fever, headache and back pains and followed by an eruption which passes through the stages of papule, vesicle, pustule and incrustation with a tendency to scar formation.

The incubation period is quite consistently from ten to fourteen days although in some instances it has been known to vary from six to twenty-one days. Usually the patient enjoys good health during the incubation period, but in some cases he will complain of anorexia, lassitude and chilly sensations for a day or two before the onset of the invasive stage.

The prodromal or invasive period is ushered in by the sudden onset of symptoms of a severe toxemia, and precedes the eruption by three or four days. The first symptom is usually a severe shaking chill with increase in the pulse rate, nausea, loss of appetite, dizziness, and at times delirium.

At the onset, the temperature may reach 104° or 105° F. and remains high until just before, or concomitant with the appearance of the exanthem when it usually drops to about normal and the symptoms of the severe toxemia abate.

A prodromal rash, while rare, may appear about the second day of the invasive stage and usually subsides again within twenty-four hours. In rare instances, however, it may even continue for several days after the variolous eruption has developed and may take one of several forms. The most common type is an erythematous, macular rash which very closely resembles the eruption of measles, except that it is not raised above the level of the skin and presents no infiltration. It may be localized to certain regions or generalized in distribution. The scarlatiniform eruption is not so common and affects localized areas of the body such as the thighs, inguinal region, etc. The petechial or hemorrhagic prodromal eruption has a predilection for the lower abdomen, genitals and upper aspects of the thighs, also the axillae and adjacent aspect of the arms and pectoral region. It consists of numerous pinpoint to pinhead sized violaceous or reddish colored spots so numerous that they give the skin a diffuse, reddish appearance.

Eruptive Stage.—The true exanthem appears first on the forehead, nose and mucous membranes of the mouth and nasopharynx, then the face and scalp, and soon spreads to the back, chest, arms, hands and finally the legs and feet, including the palms and soles. About two to three days are required to complete its distribution. When the eruption is fully developed, it is most marked on the head and below the elbows and knees on the extremities. More lesions are present on the shoulders and chest than the lower trunk and the extensors are usually more affected than the flexors. The eruption appears more profusely on skin which has been previously inflamed or irritated. The face is always involved no matter how mild the attack.

The individual lesion begins as a split pea sized, pinkish macule which deepens in color and increases in size, becoming indurated and papular in character and shotty to the touch. The lesions are at first discrete, but if the eruption is profuse, they may become confluent even before the vesicular stage. On the third day of the eruption, fluid appears in the earlier lesions and by the fourth or fifth day, all the lesions are vesicular, about the size of a split pea and very firm. Some have an oval roof, others conical, while still others are flat

topped and may show an indentation on the surface that represents the opening of a hair follicle or sweat duct. Most of the lesions are surrounded by an erythematous halo. Some of the larger vesicles may present a larger, round or irregularly shaped depression or umbilication which is probably produced by the peripheral bulging of the pock and is thought to be of diagnostic importance. One can sometimes observe vertical septa through the roof of the large, clear vesicles which divide the interior of the lesion into compartments and account for its multilocular character.

Suppurative Stage.—The fluid of the vesicles gradually becomes cloudy until on about the sixth day of the eruption it is actually purulent and grayish or yellowish in color. The large umbilicated pustules become globular due to a destruction of the epithelial strands that hold down the center of the vesicles, and the lesions now stand out conspicuously from the skin. The surrounding areola changes to a darker red or a violaceous hue. On the face and scalp where the eruption is apt to be most profuse and confluent, there is frequently a diffuse redness and marked swelling or tumefaction of the part, sufficient at times to close the eyelids and produce a swelling of the face beyond all recognition of features.

The pustular lesions are first seen on the face and scalp where the oldest lesions are present, consequently one might find vesicular lesions over the trunk and extremities and pustular lesions on the face. During the pustular stage the temperature rises and the toxic symptoms recur but quickly recede after the pustules begin to drain. The inflammation and swelling subsides, restoring the swollen features to normal contour.

Stage of Desiccation.—On about the eighth day of the eruption the lesions begin to retrogress. They become dry, shrivelled and many erupt to exude a dirty yellow, sticky pus that dries to form a brown crust and produces a foul, offensive odor. Other lesions will rupture in the center, dry and form a cup-shaped depression known as "the secondary umbilication," and is commonly seen on the dorsum of the hands. On the palms and soles the smallpox vesicles dry to form a dark brown colored crust that may remain for some time before desquamation (Fig. 143).

The crusts become detached and are cast off by the third or fourth week leaving small depressions or granulating areas. The degree of scar formation depends upon the depth of the inflammatory destruction. As a rule, only a small percentage of the lesions leave noticeable scars.

The stage of incrustation is often accompanied by intense itching and at times it becomes almost impossible for the patient to refrain from scratching.



Fig. 143.—Smallpox lesions showing the pustular stage of development, the erythematous halo surrounding the pustule, the umbilication and the presence of the pustules on the soles of the feet. (Courtesy of Dr. Louis Koplik)

The mucous membrane lesions are seldom as numerous as those on the skin, and are mostly confined to the orifices to which the air has access, such as the mouth, nose and pharynx, only rarely the larynx, bronchi and esophagus. The mucous membrane lesions begin as pinhead sized or larger, intensely red macules that soon become papular and present a white, glistening center. They are soon eroded by the action of the

mucous secretions and assume a grayish appearance with little or no elevation and are sometimes superficially ulcerated. The tongue may be involved with a rather painful glossitis and frequently the mucous membranes are so painful that solid foods cannot be taken.

Secondary toxic rashes occasionally occur between the eighth and eighteenth day over the trunk and extremities, and may be merely a diffuse, dusky redness; a scarlatiniform erythema or any erythematous mottling of the skin. These rashes last only two to three days and may be accompanied by a slight rise in temperature.

It may be well to state here that the smallpox lesions are infectious during their entire development and until all the scabs have fallen off. The most infectious period is during the pustular and incrustation stages. The disease, however, is contagious during all stages characterized by symptoms.

Varieties of Smallpox.—*Varioloid* is a mild form of the disease usually occurring in vaccinated people who have lost some of the protection of this immunity.

Alastrim (Amaas) is a mild form of the disease, occurring in unvaccinated people.

Confluent smallpox (*variola confluens*) is a term used to designate an extensive form of the disease where a confluence of lesions is marked.

Hemorrhagic smallpox (black smallpox) is divided into two types: (1) *purpura variolosa* is the most malignant type and is commonly fatal before the sixth day. The incubation period may be shortened to a week, and the onset of symptoms is violent and severe. A hemorrhagic and purpuric eruption usually appears by the second day and is associated with hemorrhages from the mucous membranes. (2) *Variola pustulosa haemorrhagica* is the more common type of the hemorrhagic form and is less fatal. It is characterized by hemorrhage into the smallpox lesions and may develop during the papular, vesicular or pustular stage. Hemorrhages from the mucous membranes are common.

Cutaneous Complications.—The cutaneous complications of smallpox are the result of a secondary infection of the variolous lesions and usually occur during the pustular or incrustation stage.

The most common type is impetigo variolosa which occurs during the period of desiccation as a yellowish colored bleb that spreads peripherally from the crusted pock. It may attain the size of a silver half dollar and forms a yellowish colored crust after the bleb has ruptured.

Furuncles frequently develop after the incrustation stage, and occur even in mild cases. Carbuncles are rarely seen but may appear during convalescence.

Subcutaneous abscesses may occur over any part of the body but have a predilection for the head and arms. They are seen mostly in the cases that develop furuncles and may be preceded by a cellulitis of the skin and subcutaneous tissues. These areas fluctuate in a few days and often reveal an extensive undermining abscess which occasionally is complicated by a fatal septicemia.

Gangrene is rare but, when it does develop, is usually seen during the second week. It may affect any part of the body but is most commonly seen on the scrotum where it begins as an edematous infiltration which soon becomes necrotic and results in considerable tissue destruction. In confluent cases of smallpox, multiple areas of gangrene may occur on the face following the swelling and inflammation of the skin or they may be secondary to subcutaneous abscesses.

Erysipelas, although rare, most commonly develops on the face and is accompanied by a high fever. The streptococcus enters through abrasions or through the smallpox lesions.

Differential Diagnosis.—*Measles* may be confused with the prodromal morbilliform eruption of smallpox, but the latter lesions are not elevated, have a predilection for the trunk and extremities, and appear on the second day of the prodromal stage and fade within twenty-four hours.

The early eruptive stage of the confluent type of smallpox may also resemble measles but the preeruptive symptoms of smallpox are usually more severe and the temperature drops soon after the eruption appears, while in measles it continues high. The suffusion of the eyes, the respiratory symptoms and the Koplik spots so constant in measles are absent in smallpox. The variolous eruption consists of hard, shotty papules while in measles the eruption is soft to the touch and consists of large, discrete and conglomerate maculopapules.

Syphilis is well known as the "great imitator" and makes no exception in the case of smallpox, but here again the constitutional symptoms are not severe. The distribution may be identical, but in the pustular syphilid, the trunk is most extensively involved while the palms, soles and lips are rarely, if ever, affected. The course of a syphilitic eruption is chronic while the smallpox lesion changes rapidly from day to day and the blood Wassermann reaction in secondary syphilis is positive.

Drug eruptions may simulate smallpox, but there is an absence of the severe constitutional symptoms.

Chickenpox.—The differential diagnosis is discussed with that disease.

Pemphigus although resembling at times mild cases of smallpox, usually offers no diagnostic difficulty.

Meningitis.—A purpuric eruption of the body may occur in the cerebrospinal type of meningitis and is accompanied by violent headache and delirium. The retraction of the head, rigidity of the neck, and positive Kernig's sign are usually sufficient to distinguish this condition.

Typhoid Fever.—The rose spots of typhoid fever may sometimes resemble the early eruption of smallpox, especially during an epidemic of the latter, but the insidious onset of the febrile symptoms and the fact that the lesions occur mostly on the abdomen and do not develop beyond the macular or maculopapular stage is sufficient to distinguish it from variola.

Typhus Fever.—In this condition, a macular and maculopapular eruption often develops but is seldom present on the face and does not undergo the evolution of the smallpox lesions.

Local Treatment of Smallpox.—During the vesicular stage, the patient often experiences considerable itching, burning and even actual pain in the lesions. For this, simple antipruritic remedies are usually sufficient: calamine lotion with $\frac{1}{2}$ per cent phenol and $\frac{1}{4}$ per cent menthol or camphor, or the application of vaselin or cold cream containing 1 to 3 per cent phenol and $\frac{1}{2}$ per cent camphor or menthol. Equal parts of olive oil and lime water are also suggested. When the symptoms are distressing, cold compresses often give tremendous relief while at other times, warm compresses are more comforting.

During the pustular stage, the purpose of treatment is to overcome the foul odor and prevent secondary infection.

To lessen odor, a dusting powder of boric acid or 10 to 20 parts of iodoform or aristol in 100 parts of talcum is very effective.

The iced or warm compresses and continuous warm baths are also very comforting.

Schamberg and Kolmer used daily baths of 1:500 creolin or 1:10,000 corrosive sublimate; kept the patient immersed fifteen to twenty minutes daily, then dusted over with an antiseptic powder. They also recommend painting the lesions daily with tincture of iodine or the use of mildly antiseptic ointments such as 1 to 3 per cent ammoniated mercury. The baths assist in softening the crusts and relieving the collection of pus beneath.

For the eyes, compresses of warm boric acid solution and the application of boric acid ointment to the margin of the lids is advisable. The conjunctival sac should be irrigated frequently with boric acid solution, especially if the margins of the lids are envolved.

The mouth should be cleansed several times a day with a mild antiseptic mouth wash or saline or bicarbonate of soda solution. When there is considerable pain from the eroded lesions, a mouth wash made by dissolving one 5-grain aspirin tablet in $\frac{1}{2}$ glass of warm water will often relieve the pain while eating.

CHICKENPOX

(Varicella)

Definition.—Chickenpox is an acute, highly contagious disease occurring chiefly in children and characterized by an eruption of macules, papules, vesicles and pustules appearing in crops and accompanied by mild constitutional symptoms.

The incubation period is usually fourteen to sixteen days although it may vary from seven to twenty-one days.

In general, a true prodromal stage in children is extremely rare but not so unusual in adults. Some children will have a slight rise in temperature with anorexia, vague pains and chilliness for a day or two before the eruption; in others, only a restlessness is noted. In adults the symptoms may be more marked.

A prodromal erythematous or scarlatiniform rash may, in rare instances, be seen a day or two before the appearance of the true eruption. It may be localized to the trunk or universal in extent, usually disappearing within twenty-four hours and often associated with a slight rise in temperature and even malaise.

The Eruptive Stage.—Concurrently with the appearance of the eruption or within a few hours before or after, there is a varying degree of fever. It may be no higher than 99° F. but in some cases it reaches 104° to 105° F. and usually subsides within twenty-four hours to 99° or 100° F. and drops to normal within one to three days. Other times, however, the temperature may not return to normal for several days, and if the varicellous lesions become secondarily infected, the temperature may again rise for a week or two, depending upon the severity and extensiveness of the eruption.

The location of the eruption may vary somewhat in different cases but is usually surprisingly uniform in its centripetal distribution, being most profuse on the trunk and sparsely scattered over the extremities, rarely occurring on the hands and feet, although vesicles are occasionally seen on the palms and soles. The scalp and face are nearly always involved.

The first lesions usually develop on the trunk, face or scalp. They then appear in successive crops to involve other parts of the body. Some cases only present a few lesions during the entire disease, others are extensively attacked, several hundred lesions being present. The lesions remain discrete throughout their course.

Vesicles may appear on the mucous membrane of the mouth where the soft and hard palates are the most common locations and usually precede the skin eruption by a few hours. Vesicles in the mouth soon rupture and appear as small grayish erosions or ulcers with a surrounding inflammatory halo, closely resembling aphthous ulcers. The conjunctival surface of the eyelid is sometimes attacked and is accompanied by considerable pain and swelling of the lid. In women, lesions have been reported on the mucous surface of the vulva and are quite painful if situated near the urethral orifice.

Ordinarily when one observes a case of chickenpox, only vesicles, pustules and crusted lesions are seen, but in the early

cases, one may observe the initial lesion which is a split-pea to bean sized, round, reddish macule, not unlike the rose spot of typhoid. The lesion rapidly becomes papular or the central portion becomes raised and a small, clear, "dew drop" vesicle appears at the apex. The vesicles enlarge to attain a size varying from that of a pinhead to a bean. They are tense to palpation but not so hard as the lesions of smallpox. The roof of the vesicle is thin and easily ruptured by friction or scratching.

The fluid content of the vesicles is at first thin and water-clear but soon becomes turbid and later purulent in character. The color varies from the clear "dew-drop"-like appearance of the early vesicle to that of a milky or yellowish color as the fluid becomes more purulent.

The lesions are usually round or oval, but their shape may be somewhat influenced by the lines of cleavage of the skin. Many of the vesicles are surrounded by an inflammatory halo.

Some of the vesicles show a slight umbilication in the center (primary umbilication). This is especially true of those which have a hair piercing the center of the lesion. After twenty-four to forty-eight hours, the vesicle loses some of its tenseness and a central depression forms (secondary umbilication). With a further loss of fluid a yellowish-brown to dark brown, firmly adherent and thin crust develops. Within two to four days the crust contracts and loosens at the edges falling off within two to three weeks, leaving only a slightly reddened area that soon disappears without noticeable scar formation.

Some of the lesions involute without developing beyond the macular or papular stage while others will incrustate from the small vesicle stage. About one to three days are required for the lesion to develop from the macule to the stage of incrustation and as there are new crops of lesions appearing for the first four to five days, lesions in all stages of development may be seen at one time. It requires about two to three weeks from the onset of the eruption for all the crusts to be cast off.

Scars from chickenpox are seldom numerous, and are a result of the destruction of the papillary layer of the true skin. This is usually caused by scratching and secondary infection but can also occur during the uncomplicated involution of the

lesions. Keloids have been known to develop at the site of necrotic lesions.

Cutaneous Complications and Sequelae.—*Impetigo varicellosa* is a secondary impetiginous infection of the chickenpox lesion which spreads in the same manner as the impetigo of the smallpox lesion. It is most commonly seen in lesions that have been scratched.

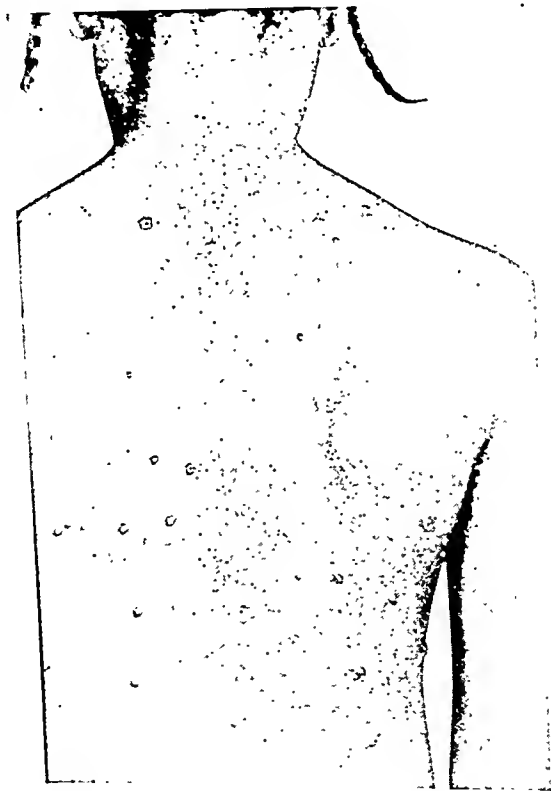


FIG. 144.—Chickenpox, showing distribution of the eruption; lesions in different stages of development and umbilication.

Boils and subcutaneous abscesses are also a result of secondary infection and are most frequently seen on the scalp.

Erysipelas may begin around the pock and fatal cases have been reported.

Cutaneous gangrene may occur in the individual lesions or several necrotic lesions may coalesce to form ulcers of varying

size with necrotic crusts that are surrounded by a dark red inflammatory zone beyond the advancing border. The temperature may rise to 104° or 105° F. and pulmonary infarcts are not uncommon in extensive cases although mild cases usually recover.

Differential Diagnosis.—*Smallpox.*—As a rule, chickenpox can be readily distinguished from smallpox but mild cases of smallpox and severe cases of chickenpox may offer diagnostic difficulty even to the experienced. The main points of diagnostic importance are as follows:

The prodromal stage of smallpox, which lasts three to four days, is characterized by severe constitutional symptoms such as chills, fever, headache, prostration and general pains, while in chickenpox there is usually no prodromal stage, or if present, it is only noticed twelve to twenty-four hours before the eruption and then it is mild in character.

The distribution of the smallpox eruption is characteristically more profuse on the face and distal part of the extremities being sparse on the trunk, while in chickenpox the eruption is most prevalent on the trunk, especially the back, and the lesions are few on the extremities. The palms and soles are rarely attacked in chickenpox.

The smallpox lesions begin as hard, shotty papules that develop into firm, thick-walled vesicles, then pustules. They have a more infiltrated base and are deeper seated than the lesions of chickenpox. The vesicles of smallpox are multilocular and difficult to empty if pricked with a needle. The chickenpox vesicles are thin roofed, easily broken and more apt to be unilocular in character.

The lesions of chickenpox appear in successive crops so that lesions are seen in various stages of development from the vesicle to the crusted lesions and only two to four days are required for the vesicle to form a thin friable crust, while in smallpox the lesions show a uniform development in any given area and require ten to twelve days (occasionally six days) for their evolution and then form a thick, compact and hard brownish crust.

Generalized Herpes Zoster.—Accompanying any case of herpes zoster there may be a few aberrant vesicles scattered over the body and occasionally there are numerous vesicles ap-

pearing over the body that are indistinguishable from the eruption of chickenpox except that they usually appear in one crop and disappear within a week. Some believe these are cases of chickenpox associated with herpes zoster. One of us (L. B.) has a series of 7 such cases, all appearing in adults who had had chickenpox during childhood. It is quite likely they are part of the herpes zoster syndrome although it is generally believed that there is a close etiological relationship between the two diseases.

Local Treatment.—The fingernails should be kept short to minimize the chances of trauma and secondary infection from scratching. Daily sponge baths should be given and care must be exercised not to rupture the vesicles or remove the crusts by rubbing. If itching is present the same local treatment may be used as suggested for smallpox. Complications are treated as the individual case requires.

MEASLES

(Morbilli)

Definition.—Measles is an acute, contagious, febrile disease occurring mainly in children, and characterized by catarrhal symptoms of the respiratory tract, conjunctivitis, and a confluent, macular eruption.

The incubation period is quite consistently from ten to twelve days, although in some instances periods of seven to fourteen days have been reported. If immune globulin or convalescent serum is given for the modification of measles after exposure, the incubation period may be prolonged to a maximum of twenty-one days.

The prodromal or invasive period is commonly four days but may be as long as six days in some cases. A prodromal eruption, while rare, is occasionally seen in measles any time from the first to the third day of the invasive stage and takes the form of a faint erythema, limited mainly to the trunk and limbs; or a rather diffuse scarlatiniform eruption which is sometimes confused with scarlet fever. The prodromal rash usually disappears in twenty-four to forty-eight hours.

The onset of the prodromal period is usually gradual and less severe than that seen in smallpox. The symptoms frequently follow in a characteristic chronological order. The first symptom is usually fever which may take one of several

forms, being only slight at first, rising to 104° F. at the onset of the eruption; or the temperature may rise abruptly to 103° F. or more and remain high with morning remissions until the development of the rash; while still other cases may show no temperature rise until just before the appearance of the exanthem when it will rise to 101° or 102° F. In all cases, the temperature usually falls by crisis or rapid rises soon after the rash has fully developed.

Within a few hours after the temperature rise, the eye symptoms become manifest and consist of lacrimation, varying degrees of photophobia, and puffiness of the lids with or without conjunctivitis.

Symptoms of a catarrhal inflammation of the upper respiratory tract usually follow next in order and consist of sneezing, nasal discharge, hoarseness, and often a high-pitched cough. The throat is red, and headache, irritability, anorexia, and drowsiness are often present.

Koplik's spots, which are the most pathognomonic features of the disease, usually make their appearance on about the second or third day of the prodromal period. Sometimes they appear simultaneously with the exanthem and are present in over 90 per cent of the cases. These lesions appear as pin-head sized, or slightly larger, bright red spots on the mucous membrane with a pinpoint sized bluish-white speck in the center. They may be numerous or only a few in number and usually appear first on the inside of the cheeks, opposite the first molar teeth. As they increase in number, the entire inside of the cheeks, and in rare instances, the mucous membrane of the lips, gums and vagina may be involved. They are at first discrete, but as they retrogress they lose their individual character in a diffuse redness of the cheek with the tiny white specks studded over the surface. The Koplik's spots usually disappear soon after the exanthem develops.

Lesions of the true exanthem may also appear in the mouth, on the hard and soft palate, and on the cheeks. They may appear a day or two before the cutaneous eruption as small irregularly shaped, rose colored spots, often slightly raised above the mucosa, and, at times, develop a central pinpoint sized vesicle which becomes raised above the lesion, giving it a summit-like appearance. They do not, however, develop the

milky white speck in the center like the Koplik's spots and they are not pathognomonic of measles but may occur in other exanthemata.

During the development of the eruption there is an increase in severity of the constitutional and local symptoms. The eyes become swollen, red, photophobia is increased, the nasal discharge is more profuse, the voice is hoarse and the cough often disturbing. The throat is red, and there may be enlargement of the lymph glands at the point of jaw. With the full development of the eruption which required three to four days, these symptoms subside except for the cough which may persist for a week or two.

The exanthem usually appears first on the sides of the neck, forehead, cheeks or chin, then spreads to the trunk and upper extremities, and by the third day the legs are involved. The rash usually fades in the order of its appearance. When the eruption is fully developed, the face, back and chest are most profusely affected, and the face often assumes a dusky, swollen appearance.

The lesions begin as pinhead to bean sized slightly elevated macules which take a variety of shapes. They are sharply margined and dull red to reddish brown in color. Some take on a bluish hue, especially over the dependent parts of the body. The macules are at first discrete, but as they increase in size and number, they coalesce in areas to form irregular confluent patches that stand out in bold relief against the pale normal skin, producing a blotchy appearance. In some instances, segments of circles or crescent arrangements of the lesions may be seen. In general, the measles eruption lacks uniformity and symmetry.

The lesions do not always remain as slightly elevated macules but distinct papules may be present and at times, miliary vesicles develop at the summit of the papules, imparting a "prickly-heat"-like appearance. In other cases small pinhead sized papules may develop about the hair follicles. The above variations of lesions may appear in any case of measles but definite types are most likely to be constantly present in certain epidemics.

The hemorrhagic form of measles is caused by hemorrhages into the lesions, imparting a purplish or bluish color which

does not disappear under diascopic pressure, and during involution goes through the various color changes of an ecchymosis. A few of these lesions may be observed during the evolution or involution of any measles eruption or when measles is complicated by pertussis. They are seen most extensively, however, in the malignant type of measles which is accompanied by severe constitutional symptoms and one may observe varying sized ecchymoses into the skin, petechial spots,



Fig. 145.—Measles eruption showing the macular confluent character of the lesions.

and at times a bloody discharge from the mucous membranes. Blood may also appear in the urine, stool and vomitus. These cases are fortunately very rare and were referred to as black measles.

Brownish, pigmented spots are frequently seen after the measles eruption disappears and correspond in size and shape to the original cutaneous lesions. This pigmentation usually fades within a week or ten days.

Desquamation.—A fine, branlike or furfuraceous scaliness often occurs as the rash begins to fade and is seen first on the face and neck, seldom occurring on the hands. This scaliness is not noticeable in all cases, but varies with the severity of the eruption and it is usually completed within a week.

There may be a marked variation in severity of both the constitutional symptoms and the eruption, and even anomalous cases may develop during an epidemic. Cases have been reported as occurring without fever, others without the catarrhal symptoms while still others develop normally up to the eruptive stage including the Koplik spots and then fail to develop the exanthem. Cases treated with convalescent serum or placenta tissue extract often have mild symptoms.

Complications.—Most of the severe complications of measles are those of the respiratory tract or the central nervous system. The cutaneous complications are not usually severe and occur mostly in debilitated persons whose resistance has been lowered by other diseases such as tuberculosis, diabetes, etc.

Herpes facialis occurs as in many other febrile conditions.

Urticaria may occur during the disease or after the symptoms have subsided.

Bullous eruptions have been described as occurring before, during or following the exanthem, the blebs varying greatly in size. They come out in crops on the skin and mucous membranes and may be accompanied by fever.

Boils and subcutaneous abscesses may occur during the convalescent stage.

Disseminated tuberculosis is well known to follow attacks of measles and is caused by the dissemination of a tuberculous pulmonary lesion.

Gangrene, while rare, may be a serious complication of measles. It most often affects the mouth and cheeks and may be accompanied by an ulcerative stomatitis. It usually begins just behind the commissure of the mouth as a violaceous colored blister which enlarges. The cheek becomes hard and swollen and a dark red area of necrosis develops in the center. The necrotic area spreads peripherally behind an advancing dark red, infiltrated and vesicular border that is slightly raised above the surrounding skin. An extensive area of tissue may

be destroyed before a line of demarcation is formed and subsequent healing takes place.

Differential Diagnosis.—*Rubella* (German Measles).—In this disease, the stage of prodromal symptoms is very brief (seldom more than twenty-four hours), the catarrhal symptoms are slight or absent even in the severe cases, and the fever is seldom above 101° F. and of short duration. There are no Koplik's spots as in measles. The eruption spreads more rapidly and is of shorter duration than measles and the lesions more discrete, papular, and not so dark in color. The constitutional symptoms are mild and there is an enlargement of the postauricular lymph glands.

Scarlet Fever.—The onset of scarlet fever is more severe with high fever and vomiting. The eruption appears on the second day and the catarrhal symptoms and photophobia of measles are absent. There is a painful, sore throat and enlargement of the submaxillary and cervical lymph glands and the characteristically swollen, red, strawberry tongue. The face is not so profusely affected by the rash as in measles and it has a punctate bright red appearance. There is usually a circumoral pallor and Koplik's spots are absent.

Smallpox.—Described under that disease.

Syphilis.—The macular type of syphilis, in adults, when accompanied by constitutional symptoms may be confused with measles especially when it occurs during measles epidemics, but when one considers the slow evolution of the syphilitic macular eruption and the fact that the macular lesions are not swollen, usually discrete and seldom involve the face, there is not so much chance for confusion.

Drug Eruption.—Antipyrine, luminal, quinine, chloral, copaiba and sulfanilamide are the drugs most liable to produce eruptions that are confused with measles, especially copaiba. In general, drug eruptions appear more profusely on the trunk and, if extensive, do involve the face. They characteristically produce marked itching and are bright red in color except the copaiba eruption which is dark red in color. They may coalesce to form patches but lack the catarrhal and photophobia symptoms and although mouth lesions are present, the Koplik spots are absent. Mild temperature reactions may be present but are not common.

Local Treatment.—The mouth should be washed several times a day with a warm alkaline mouth wash. If an ulcerative stomatitis develops, diluted Dobell's solution or hydrogen peroxide irrigations should be used.

The skin should be kept clean with sponge baths of soap and water. The itching can usually be relieved by the application of equal parts of camphor water and rose water, but if severe, calamine lotion containing $\frac{1}{2}$ per cent phenol and 10 per cent olive oil is very soothing. When pyogenic infections develop, 1 to 5 per cent ammoniated mercury ointment should be applied to the infected areas.

GERMAN MEASLES

(Rubella)

Definition.—An acute, contagious disease of specific character, lasting three to four days and characterized by mild constitutional symptoms, swelling of the posterior auricular and cervical glands and an eruption of scattered rose colored macules that are slightly raised above the level of the skin.

The incubation period ranges from five to twenty-one days and apparently varies with different epidemics. In most cases, there are no symptoms during this period.

The prodromal stage lasts anywhere from a few hours to five days. Constitutional symptoms, if present, are very mild and consist of malaise, headache, anorexia, slight cough and perhaps a temperature of 100° F. The exanthem is usually the first evidence of the disease.

The eruption commonly makes its appearance first on the face and spreads in a few hours to involve the head, trunk and extremities. This sequence of involvement is by no means constant. The eruption may first appear on other parts of the body and spreads very rapidly. It is not unusual to see the rash more fully developed on the face and chest than on the lower extremities, and the later areas show the full extent of the rash when the lesions on the face are fading. The duration of the maximum intensity of the eruption may be only a few hours to a day.

Typically, the eruption consists of numerous small, reddish-pink colored, rather discrete and slightly raised, scattered macules. They are barely raised but can be palpated.

They are usually round or oval but may be irregular in shape. The lesions are much lighter in color than the darker red macules of measles and are also smaller, more discrete and more regular in outline. If the eruption becomes profuse, the lesions may coalesce to form areas with a scarlatiniform appearance. As a rule, however, the discreteness of the individual pinkish lesions as they stand out against the pale background of normal skin is what gives the eruption its characteristic appearance. Pressure or friction applied to the skin increases the eruption in that particular area.

When the exanthem is fully developed, the face is most profusely affected, especially the forehead, cheeks and chin. The scalp and neck are also involved, while over the trunk and arms the lesions are less abundant and the legs are affected least of all. The backs of the thighs may present confluent patches due to body pressure over these areas.

The eruption may disappear within twenty-four hours although in some cases it remains for a week and even longer. The time apparently varies with the intensity of the disease and also varies in different epidemics.

A fine desquamation may be noticed after the rash has faded but it is not a constant feature and depends upon the severity of the eruption.

A constant and characteristic feature of rubella is a tender swelling of the lymph glands of the neck, usually the suboccipital but in many cases the postauricular and submastoid glands are also involved. There may also be slight enlargement of the axillary and inguinal glands. The glandular enlargement ordinarily lasts from two to seven days, subsiding quickly after the rash disappears and makes its appearance a day or so after the eruption.

The throat is commonly red or congested and, on the soft palate, a number of pinhead sized, reddish colored, glistening lesions may be seen as slight elevations that have no specific diagnostic significance.

Types of the Disease.—In severe cases the eruption may be morbilliform or scarlatiniform in type and be accompanied by catarrhal symptoms. These cases are unusual.

Special anomalous features of the eruption:

Miliary vesicles at the summit of the reddish macules.

Petechial spots in the skin, mouth and soft palate.

Purpuric lesions.

These features are rare and noticed in only a few lesions as a rule.

Itching, when present, is usually mild, although it may vary with the individual. Cutaneous complications are rarely, if ever, seen.

Differential Diagnosis.—The differential diagnosis of measles to which rubella bears the closest resemblance, is discussed after the former disease.

Scarlet Fever.—Rubella sometimes resembles scarlet fever but lacks the general redness of the skin, the painful sore throat and the acute constitutional symptoms. The individual red maculopapules stand out in bold relief against the pale normal skin and the circumoral pallor and strawberry tongue of scarlet fever are absent.

Treatment.—The general care of the skin as suggested for measles is sufficient for rubella.

SCARLET FEVER

(Scarlatina)

Definition.—Scarlet fever is an acute infectious disease caused presumably by certain strains of the *Streptococcus haemolyticus* and characterized by an acute onset with sore throat, pyrexia, vomiting, toxemia and followed in one to two days by a punctate erythematous eruption and later desquamation.

The incubation period varies from two to seven days with an average of four days but in rare instances it may be as short as one day or longer than seven days.

The prodromal stage is characterized by the sudden onset of symptoms. The temperature rises rapidly to 103° or 104° F. in the course of a few hours, to remain elevated until the eruption begins to fade, and then is usually followed by a gradual but steady defervescence. Mild cases may have only a slight fever, while severe toxic cases may be accompanied by fever of 104° to 106° F. In this stage the face is flushed and the skin is hot and dry.

The throat is painful particularly on swallowing. There is intense redness and edema of the mucous membranes involving

the uvula, soft palate, tonsils and pharynx. The inflamed tonsils may be covered with a thin grayish exudate or numerous grayish yellow follicles. A reddish punctate enanthem is frequently seen on the uvula and soft palate, this is similar to and precedes the eruption seen on the skin by a few hours. It may be absent in mild cases.

The tongue has a thick grayish or brown coating and the breath is foul. The tip and margins soon become denuded as does the entire surface of the tongue at the end of three or four days, leaving a smooth surface studded with red swollen



Fig. 146.—Enlarged lingual papillae in a case of scarlet fever.

papillae. This is described as the “strawberry” or “raspberry” tongue and in many instances is of considerable diagnostic importance. Milder cases of scarlet fever may not present the typical appearance of the tongue (Fig. 146).

The eruptive stage appears as a rule twelve to thirty-six hours after the onset of the illness. The rash typically presents a generalized erythema on which are pinpoint to pin-head sized erythematous, slightly elevated and conical shaped papules about the hair follicles. This gives the eruption its punctate character and imparts a feeling of roughness to the

touch. The exanthem ordinarily is seen first upon the neck and upper chest from which area it spreads rapidly to the trunk and extremities. The lesions are most numerous on the inner surface of the thighs and flexor surfaces of the joints. It reaches its maximum in two to three days and then begins to fade, disappearing in about five to seven days. There is great variation in the extent of the scarlet fever eruption and in mild cases it may be almost lacking or so brief in duration as to escape detection until the desquamation occurs.

In well-developed rashes miliary vesicles are not uncommonly found. They are small, pinhead size, and occur at the summit of the papules. They are situated most frequently on the abdomen, thighs and chest. They are so minute as to be easily overlooked but careful inspection will determine their presence.

The eruption as it appears on the face is most commonly seen as a distinct red flush. The area immediately surrounding the mouth involving both the upper and lower lips and part of the chin appears pale in contrast to the bright flush of the cheeks. This is the circumoral pallor so frequently seen in scarlet fever.

The scarlatinal rash fades when pressure is applied, but when the pressure is removed, the redness quickly returns followed, in a few seconds, by a return of the pallor which persists for one or two minutes. This reaction is not pathognomonic of scarlet fever as it may be seen in other toxic rashes.

Desquamation begins in those areas where the eruption first made its appearance, and occurs about one week after the beginning of the eruptive stage. It is usually generalized and on the face the scales are fine and branny while over the body desquamation is more likely to occur in larger flakes. On the hands and feet the exfoliation may occur in large flakes or rarely as a cast of the fingers or toes. Peeling which takes place around the tips of the fingers and toes may require several weeks before it is completely cast off. Desquamation may be so slight as to be hardly recognized or so intense that scarcely any part of the cutaneous surface escapes the process. In very rare instances the hair and nails may be shed (Fig. 147).

The duration of the desquamation varies considerably in different individuals from mild cases which last two to three

weeks to prolonged cases which last two to three months. However, the usual duration is from four to six weeks.

Hemorrhagic scarlet fever is a very severe form of the disease. The attack is characterized by hyperpyrexia, severe constitutional symptoms, petechiae and ecchymosis. Hemorrhages may occur from the mucous membranes.

An exanthem of scarlet fever may in rare instances recur one to two months after convalescence and be accompanied



Fig. 147.—Desquamation occurring on the palms and fingers following scarlet fever.

by the other symptoms of the disease. These attacks are considered to be relapses but generally are due to a fresh infection.

Complications.—The complications which may follow in the wake of a severe attack of scarlet fever usually become evident during the second or third week. The most frequent of these are otitis media, cervical adenitis, endocarditis, myocarditis, nephritis and arthritis.

The cutaneous complications associated with scarlet fever, while generally not attended by such serious consequences as the above mentioned more serious complications, nevertheless are worthy of consideration.

Herpes is frequently seen about the mouth. In cases where the exanthem has been accompanied by the formation of milium vesicles, there may be a coalescence of these vesicles forming larger ones. Bullae may be seen where secondary infection of the skin has taken place, and especially if the infection is severe enough to produce gangrene of the skin.

Eczema is frequently seen about the ears and nose as a result of irritating discharges.

Abscesses of the skin are rather infrequent complications.

Differential Diagnosis.—Well-marked cases present little difficulty in diagnosis but the mild cases which may lack many of the usual symptoms of the disease require a careful analysis. Besides the other exanthematous diseases such as measles and rubella, there are drug rashes such as sulfanilamide, atropine, quinine and mercury which may simulate the eruption of scarlet fever.

Toxic Rashes.—In this type of rash the history as well as the Schultz-Charlton blanching test will be of some assistance.

Burns.—Especially severe sunburn may produce scarlatiniform rashes.

Serum Rashes.—Here again the history is of importance together with other signs of anaphylaxis. The painful angina and strawberry tongue are lacking in serum rashes.

Acute Exfoliative Dermatitis.—The dermatitis and exfoliation occur simultaneously.

Heat rashes and rashes due to irritants such as salves, oils and clothing have many of the characteristics of a scarlet fever eruption. Absence of symptoms except the rash together with the history help in differentiating these conditions.

Diagnosis.—The Schultz-Charlton or blanching test is a valuable diagnostic aid. The test consists of injecting intradermally in an area where the eruption is newly developed 0.5 to 0.75 cc. of scarlet fever antitoxin diluted 1:100 in normal saline. In twelve to twenty-four hours the area should be observed for blanching of the rash at the site of injection. A positive test is evidence that the rash is due to the scarlatinal streptococcus. If blanching does not occur, however, the diagnosis of scarlet fever cannot be excluded because there are certain few strains of streptococci whose toxins differ from those of the usual group and therefore the antitoxin is not specific

for the invading strain. If the rash is three or four days old it may not blanch.

The Dick test is valuable in discovering individuals susceptible to the disease. The test is made by injecting intracutaneously 0.1 cc. of diluted scarlatinal streptococcus toxin. The amount of the toxin used is equivalent to 1 skin test dose of the toxin. A positive reaction is due to the action of the toxin upon the tissue cells and indicates that there is no antitoxic immunity present. Redness 1 to 3 cm. in diameter at the site of injection is considered a positive reaction. This should be observed eighteen to twenty-four hours after the injection when the reaction is at its height. The reaction then gradually fades leaving a slight pigmentation and desquamation which may persist from three to six weeks. The extent of the redness is considered to be indicative of the degree of susceptibility of the individual. The Dick test is usually positive for the first three to four days of the disease. There are occasionally cases of unmistakable scarlet fever where the Dick test is negative at the onset of the disease or remains positive for several weeks. A Dick test which changes from positive to negative during the course of the illness is indicative of scarlet fever.

Treatment of the skin during the course of the disease would mostly consist of local cleanliness and if itching or burning is present the application of calamine lotion containing 10 per cent olive oil and $\frac{1}{4}$ per cent menthol is usually sufficient to give relief. During the stage of desquamation bland oils or cold cream applied to the skin are often very soothing.

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THE TREATMENT OF SOME OF THE MOST COMMON DISEASES OF THE SKIN

IT would be impossible in a short paper to discuss in any detail the treatment of all the common skin diseases. I have therefore thought it best to select a few of the most common conditions, with which the general practitioner is familiar and most likely to meet in his everyday practice, and elaborate on their treatment.

Although x-ray therapy, in the hands of a competent dermatologist, is an excellent method of curing or alleviating many skin diseases, much can be done with the intelligent use of topical remedies and other treatment. It has been my experience that usually the general practitioner lacks interest in skin conditions. He even holds the dermatologist in disdain, and believes most dermatoses are either not very amenable to treatment or get well easily with the use of ammoniated mercury or sulfur ointment. If I can correct this attitude and arouse some interest I shall feel this paper has been worth while, aside from any practical value it may have. The conditions I have selected for discussion are acne vulgaris, seborrhea, impetigo, dermatitis venenata and dermatophytosis.

ACNE VULGARIS

This common affection may be of great importance in a young girl or boy, and the family physician should consider it more seriously. As a rule the parents and the patients are quite concerned only to have their medical adviser make light of its presence and dismiss it with the statement it will disappear in time. To my mind this is "poor medicine." We

must realize acne can and does have a marked psychological effect on an adolescent child. An inferiority complex, with backwardness and timidity, in an adult may often be traced to a neglected, untreated acne of years' duration during adolescence. The family physician should show interest in these patients and treat them. It is also important to treat acne as soon as it appears because the condition may result in scarring and a permanently poor skin. It usually takes several months to a year or more to get rid of an acne, and some cases are very recalcitrant. Therefore, while impressing on the patient the disease is curable, make him understand he must cooperate. At the same time do not give the idea the condition will disappear in a few weeks, but that it may require several months of treatment and the improvement may not be immediate.

Although acne is a local disease, and primarily due to an overactivity of the sebaceous glands, it may be influenced by many other factors. A thorough history and physical examination is therefore important, not so much from the standpoint of some organic trouble, but rather to discover any functional disturbance and correct it if present. That is, to get the patient's general health up to par. In many instances you will not find anything wrong, but there is no doubt that dietary indiscretions, constipation, indigestion, lack of rest, malnutrition, anemia, foci of infection, endocrine dysfunction, pelvic disorders, masturbation, etc., may be predisposing causes.

The patient should always be questioned in regard to the ingestion of iodides or bromides which may, even in small doses, cause acne lesions. Iodized salt is commonly used in many homes and may be the factor in the cause or the persistence of an acne. If you discover this stop its use and prescribe sodium chloride, 10 to 15 grains, in capsules or enteric-coated tablets, to be taken at least three times a day. Some dermatologists are using sodium chloride routinely in acne with what seems to be favorable results.

As for diet, do not stick to any hard and fast rule, but be guided by the individual case. Contrary to popular opinion, excess carbohydrates do not cause acne. However, in some patients certain things, as chocolate, seem to aggravate the condition. In general it is best to eliminate chocolate, rich des-

serts, white bread, tea, coffee, alcohol, carbonated beverages, hot drinks, highly seasoned and fried foods. If the patient is undernourished and lacks appetite, build him up, prescribe a tonic, increase the diet, give vitamins, etc. On the other hand in the overweight the carbohydrates and fats should be restricted. The diet in either case must be well balanced.

It has been shown that liver may be of value in pyogenic diseases of the skin. Advise eating liver several times a week along with the extract every day, especially if there is any degree of secondary anemia. If necessary, hypodermic injections with the various preparations for anemia may be given.

With the advance in the knowledge of the estrogenic substances, hormone therapy has been used in acne. The results, however, have been disappointing and I do not recommend their use routinely by the general practitioner. The cases of acne which get worse at or before the menses are usually very recalcitrant and here the hormones may be given a trial, especially if there is a clinical indication for their administration.

When, to your satisfaction, the general survey of the patient has been completed, you can proceed to the local therapy, which is probably of the greatest importance from a practical standpoint. As most patients with acne have an oily skin, topical remedies to be of value must be astringent and drying. Many of these younger patients, especially the boys, are averse to washing their faces very often. Insist on soap and warm water, followed by cold water, at least three times a day. Any of the plain, nonmedicated soaps may be used. If the ordinary soaps do not dry the skin enough, tincture of green soap can be prescribed. You must explain to the patient just what effect you are after, and that you must have his cooperation to get results. If there is too much drying and chapping of the skin the treatment can be discontinued for a day or so and the lotions made weaker. Creams are taboo and should not be used, except in certain areas, as around the eyes, the lips and the neck, where you really do not wish to chap the skin.

The well-known "lotio alba" is the remedy most widely used in acne. However, it is of value only if it causes the desired effect of chapping the skin. Do not prescribe it as "lotio alba" but write out the prescription as follows:

R̄ Zinc sulfate.....	5j-iv	4.0- 15.0
Sulfurated potash.....	5j-iv	4.0- 15.0
Rose water.....	q. s. ad 5iv	120.0-120.0
Dissolve each salt in $\frac{1}{2}$ the rose water and mix both together in a mortar, stirring constantly.		

Sig.—Apply at bedtime to the affected areas, after washing with soap and water.

The zinc sulfate and sulfurated potash are increased depending on the degree of chapping obtained and desired. The lotion is left on all night and removed in the morning with soap and water. Its effect may be increased by adding to it:

R̄ Betanaphthol.....	gr. iv-xx	0.24- 1.2
Sp. vini rect.....	5ss	15.0

If necessary a supplementary lotion may be used during the day:

R̄ Betanaphthol.....	gr. iv-xx	0.24- 1.2
Sp. vini rect.....	5 ss	15.0
Sod. hyposulfite.....	5 ss	15.0
Rose water.....	q. s. ad	120.0

Sig.—Apply to affected areas once or twice a day.

Although, as stated above, the lotion used must be strong enough for the treatment to be effective, at the same time it should not be made too unpleasant for the patient. If the skin becomes very dry and chapped it is wise to stop the lotion and use a 3 to 5 per cent sulfur ointment, in a greaseless base, for a while. Later the lotion and ointment may be used alternately.

Should these various lotions not have the desired effect of chapping the skin, the so-called Vlemminckx's solution (liq. calcis sulfurated) may be tried. It is used diluted as hot wet dressings, beginning with 25 per cent strength and increasing as required. However, with the intelligent handling of lotio alba and the other lotions it is seldom necessary to resort to this unpleasant, disagreeable remedy.

Rarely patients with acne have a dry skin, and when this is the case lotio alba cannot be used. It may be tried in very weak strength and stopped as soon as the skin gets too dry and the patient complains. Even soap is not well tolerated, and a superfatted soap may have to be used at night only. In these patients one must depend on ointments, and for this

purpose sulfur or ammoniated mercury, 3 to 6 per cent, is used, ammoniated mercury being more pleasant to the average patient. However, never use them together, and if *lotio alba* or any form of sulfur has been used, wait several days after discontinuing it before beginning the other.

R	Sulfur pot. (hydrarg. ammoniat.)....	gr. xv-5ss	1.0-2.0
	Ung. aq. rosae.....	q. s. ad 5j	30.0

Sig.—Apply to face at bedtime after washing with soap.

When there are many comedones and pustules it is best not to depend on the chapping treatment alone. They may be removed surgically and this is better done by the physician than the patient. With the aid of a pointed scalpel and a comedone extractor the blackheads can be expressed and the larger pustules evacuated. However, this should not be overdone and it is not necessary to eradicate the entire condition at one visit.

If the patient can come in at regular intervals, ultraviolet light may be of value. A mild erythema dose is given and gradually increased depending on the reaction. This is repeated once or twice a week or every five days. At the same time vaccines may be used, but it must be admitted they are of little or doubtful value in acne. A mixed stock vaccine, made from the acne bacillus and staphylococcus, is generally used, although an autogenous vaccine might be preferable. It is given hypodermatically once a week or every five days, in gradually increasing doses, beginning with 0.1 cc. and increasing 0.1 cc. as tolerated, and must be continued for several months.

The scalp should always be inspected in acne. Dandruff (seborrhea) is often present and may be an etiologic or contributory factor. As a general rule the scalp, even if there is no seborrhea, should be washed once a week with any ordinary soap. If the hair is very dry it may be done every ten days or two weeks. On the other hand where the hair gets oily in a few days, which is the usual case in patients with acne and dandruff, the scalp may require washing twice a week and green soap used for the shampoo. In females shampooing may be a problem because of its effect on the "wave" of the hair, but it must be done and the patient allowed to wave the hair, or get an artificial wave.

It is easier and more pleasant to use a lotion than an ointment in the treatment of seborrhea of the scalp. As a routine do not put an oil in the lotion if the hair is dry, because the daily application of an oily lotion will make the hair quite greasy in a few days. It is better the patient apply a little oil or plain liquid petrolatum when necessary. The lotions will vary according to the color of the hair and the type of seborrhea.

Scalp lotion for dark hair

R̄	Resorcin.....	5j-ij	4.0- 8.0
	Ac. salicylic.....	5j-ij	4.0- 8.0
	Zinc sulfocarbolate.....	5ij	8.0
	Ol. violet (for females).....	gtt. v-x	
	Ol. bay (for males).....	gtt. v-x	
	Alcohol.....	5ij	90.0
	Aquae.....q. s. ad	5viij	240.0

Sig.—Apply to scalp daily and rub in with fingers.

If the hair is oily, omit the water and make up the lotion to 8 ounces with alcohol alone. In blondes and patients with light hair, resorcin cannot be used as it discolors the hair. You may then substitute resorcinol monoacetate or leave it out entirely. In very light hair it is probably safest not to use any resorcin preparation.

For very dry hair, if it is absolutely necessary to have an oily liquid, add ol. ricini (5ij-5ss) to the lotion, or prescribe a "brilliantine."

Brilliantine

R̄	Ol. ricini.....	5ij-5ss	8.0-15.0
	Ol. violet.....	gtt. v	
	Alcohol.....q. s. ad	5ij	60.0

Sig.—Apply to scalp as necessary.

The night before the shampoo an ointment is rubbed into the entire scalp and washed out the next morning. Have a thin ointment base so it will wash out easily.

R̄	Sulfur pot.....	5ss-j	2.0-4.0
	Ac. salicylic.....	gr. xv-5ss	1.0-2.0
	Adep. benzoinat....	q. s. ad	5j
			30.0

Sig.—Apply to scalp at night and wash out in the morning.

Along with these topical remedies, ultraviolet light to the scalp may be of value, especially when there is itching or loss of hair.

SEBORRHEIC DERMATITIS

This term is used for the eruption on the face, especially the eyebrows, nasolabial folds, and cheeks, behind and in the ears, the chest and upper back, associated with seborrhea (dandruff) of the scalp. In fact the scalp is considered to be the focus and origin of the eruption on the glabrous skin.

The remedies and outline of treatment given in the preceding paragraphs on the care of the scalp in acne may all be used here. However if one is not treating acne but seborrhea alone, mercury can be substituted for the sulfur. It is just as efficacious but is not prescribed in acne because of the possibility and danger of combining with the sulfur in the lotio alba and causing a formation of black mercuric sulfide.

Mercurial Scalp Lotion

R̄	Resorcin (or resorcinol monoacetate) ..	℥j-ij	4.0 -8.0
	Ac. salicylic.	℥j-ij	4.0 -8.0
	Hydrarg. bichlorid.	gr. ij-iii	0.12-0.18
	Alcohol.	℥iiij	90.0
	Ol. violet.	gtt. v	
	Aquae.	q. s. ad ℥viiij	240.0

M. and filter clear.

Sig.—Apply to scalp daily.

R̄	Hydrarg. ammoniat.	℥ss-℥j	2.0-4.0
	Ac. salicylic.	gr. x-xxv	0.6-1.5
	Adep. benzoinat.	q. s. ad ℥j	30.0

Sig.—Apply to scalp at night and wash out in the morning.

For the eruption on the face, ears or chest the following ointment is used:

R̄	Hydrarg. ammoniat. (sulfur pot.) ...	gr. xv-℥ss	1.0-2.0
	Lanolin.	℥ij	8.0
	Petrolati.	℥ij	8.0
	Ung. aq. rosae.	q. s. ad ℥j	30.0

Sig.—Apply to areas several times daily.

If the condition is acute and there is exudation, which happens particularly behind the ears, it is necessary at first to use wet dressings of Burow's solution (diluted 1 to 6) and later a paste such as:

R̄	Hydrarg. ammoniat.	gr. xv	1.0
	Zinc paste.	q. s. ad ℥j	30.0
or			
R̄	Hydrarg. ammoniat.	gr. xv	1.0
	Liq. burowi.	℥iss	6.0
	Lanolin anhydr.	℥iiij	12.0
	Zinc paste.	q. s. ad ℥j	30.0

When the acuteness and exudation have disappeared you may then switch from the pastes to the ointment as given above.

As most patients with seborrhea have an oily skin soap and water should be used for cleansing. If the scalp is crusted an oil is first applied to remove the crusts before beginning the lotions and ointments. For this purpose salicylic acid (2 to 3 per cent) in olive oil is used. It is washed out with soap and water.

Ultraviolet light, in suberythema doses, may be of value, and is given twice a week to the various areas. As for general treatment, the routine outlined in acne should be followed. Recurrences in seborrhea are common and it is wise to continue treatment of the scalp even after the eruption in the other areas has disappeared.

IMPETIGO CONTAGIOSA

In the treatment of impetigo, ammoniated mercury or sulfur is practically specific. For reasons given above I prefer to use mercury. Although most general practitioners know this, they have trouble with impetigo for two reasons. In the first place they usually prescribe the U.S.P. ointment, which is 10 per cent and apt to cause a dermatitis. The other pitfall is the method of application of the ointment and the directions given the patient.

It is most important to first remove the crusts. This can readily be done with soap and water, either by ordinary washing or poulticing if necessary. In fact, washing with soap and water is very valuable and should be repeated several times during the day. To prevent autoinfection and new lesions a bichloride of mercury solution (1:4000) can be sopped on after drying. Then the ointment is applied to each lesion and left on continually. In infants and children begin with a 2 to 3 per cent ointment, in adults 5 per cent. It may be increased if there is no sign of irritation and not enough improvement in a few days. Should the eruption be widespread, it is well to remember the danger of mercurialism, although I have never seen a case of mercurial intoxication from absorption in the treatment of impetigo.

The disappearance of the eruption can be hastened considerably by the use of a 2 to 3 per cent copper sulfate solution. After the crusts have been gently removed with forceps, the oozing surface is sponged dry and the copper sulfate solution applied with a cotton applicator. This is repeated every day. The ointment is used just the same, applied after the painting and left on. If the patient is able to come into the office, this is best done by the physician, and lesions hidden to the patient, as inside the ears, are not missed and do not continue to be a source of reinfection. With the combined use of ammoniated mercury and copper sulfate, impetigo is usually cured within a week.

Ultraviolet light has some antiseptic properties and may be of value in impetigo. The crusts are first removed and very mild erythema doses given every day.

It is well to think of pediculosis in impetigo in children and inspect the scalp for nits. Directions should be given regarding contact and sources of infection such as towels, shaving utensils, powder puffs, clothing, bedding, household animals and swimming pools.

DERMATITIS VENENATA

As this is an inflammation of the skin due to some external irritant it is most important in treatment to first attempt to discover the cause of the eruption in each particular patient. With experience this can often be done by a careful history and sometimes by the clinical appearance and location of the eruption. Although this paper is not concerned with diagnosis, I shall discuss it briefly from that angle because it really is so important a part of the treatment.

The causative agent may be anything at all to which the patient is or has become susceptible. The dermatitis may be due to a primary irritant, that is, some substance which would produce a dermatitis on almost any skin, or it may have been caused by a substance which the patient has come in contact with for a variable period of time, without any ill effects, and then suddenly become sensitive or allergic to it. The latter is usually the case. One must therefore not think because a patient has been in contact with a certain substance in his occupation for many years or a woman has been using some

cosmetic preparation for a long time that it cannot be the cause of the dermatitis. As the diagnosis is a problem in detection, one must, like a good detective, not overlook any clue, and lay the blame on any suspected cause until proved otherwise. For this purpose the so-called "patch tests" are of the greatest value, but here again one must not acquit a substance just because the patch test is negative. A face powder may cause a dermatitis of the eyelids and still give a negative patch test on the forearm. However, while investigating, eliminate any suspected substance although the test is negative.

The treatment of dermatitis venenata depends on the type and stage of the eruption. It is here the fundamentals of skin therapeutics must be known to get good results. One should not prescribe a drying "calamine lotion" or an ointment for an exudative crusted skin. Whatever you prescribe should be soothing. It goes without saying you surely do not need an antiseptic ointment, as ammoniated mercury or sulfur, to cure a dermatitis due to an external irritant.

For the simple dermatitis with just erythema and no exudation, a soothing lotion to use during the day, and a bland ointment at night usually suffice. I do not recommend prescribing or telling the patient to get "calamine lotion."

Soothing Lotion and Ointment

R̄	Phenol.....	gtt. xv-5j	1.0 -4.0
	Liq. carbonis detergens.....	5ss-j	2.0 -4.0
	Zinc oxide.....	5ij	8.0
	Magnes. carbonate.....	5j	4.0
	Aq. calcis.....q. s. ad	5iv	120.0

Sig.—Apply to affected areas several times daily.

R̄	Phenol.....	gtt. iij-v	0.18-0.3
	Menthol (may be omitted).....	gr. j-iij	0.06-0.18
	Lanolin.....	5ij	8.0
	Petrolati.....	5ij	8.0
	Ung. aq. rosae.....q. s. ad	5j	30.0

Sig.—Apply to areas at night.

The menthol is included if there is a good deal of burning along with itching. However, be careful of menthol as it is apt to be irritating.

If the eruption is acute, vesicular and quite exudative, it is better to use wet compresses at the beginning. For this

purpose Burow's solution (liq. alum. acetate), diluted 1 to 6 with water or boric acid, is of value.

R	Liq. alum. acetatis.....	℥ij	60.0
	Sol. ac. boric.....	q. s. ad ℥xij	360.0
Sig.—Apply to areas as wet dressings.			

Along with the wet compresses an emulsion may be used, or you may change to an emulsion in a day or so.

Soothing Emulsion

R	Liq. carbon. detergens.....	℥ss-ij	2.0-8.0
	Phenol.....	℥ss-j	2.0-4.0
	Liq. burowi.....	℥j	30.0
	Zinc oxide.....	℥ss	15.0
	Magnes. carbonate.....	℥ij	8.0
	Aq. calcis.....	℥iv	120.0
Mix above very well and add			
	Ol. olivae.....	q. s. ad ℥viiij	240.0

Sig.—External use (shake well).

During the night wet applications cannot be kept wet and lotions become dry so that it is better to use a paste, such as zinc paste. I have found the following very efficacious:

R	Phenol.....	gtt. iij-v	
	Menthol (may omit).....	gr. j-iiij	
	Liq. burowi.....	℥j	4.0
	Lanolin anhydr.....	℥iij	12.0
	Zinc paste.....	q. s. ad ℥j	30.0

Sig.—Apply to areas at night and remove with olive oil.

As for internal treatment there is none except in the case of dermatitis due to poison ivy, in which it may be of value to give one or two intramuscular injections of the extract. If this is not possible the tincture can be taken by mouth.

R	Tr. rhus toxicodendron.....	gtt. xv	1.0
	Syr. auranti.....	℥ij	8.0
	Aquae.....	q. s. ad ℥iij	100.0

Sig.—(One drop in water t. i. d. p. c. and increase 1 drop with each dose. Stay at 20 drops.

The extract by injection or the tincture by mouth may also be tried as a prophylactic in persons susceptible to poison ivy.

In closing this discussion of dermatitis venenata may I add that the topical treatment of "eczema," which I purposely

omitted from this paper, is fundamentally the same as outlined above. If one grasps the essentials and knows when to use a lotion, wet dressing, ointment or paste, he is able intelligently to treat eczema, which is really an exudative dermatitis.

DERMATOPHYTOSIS

There are many remedies in the treatment of dermatophytosis or "fungous" infection of the skin. However, it usually suffices to know a few and understand when and how to use them. As there are several varieties of dermatophytosis, the treatment cannot be standardized and will depend on the particular type.

The commonest form is the interdigital, in which there is scaling and maceration between the toes, the typical so-called "athlete's foot." As you all know, Whitfield's ointment is one of the favorite remedies, and probably just as efficacious as any other in most cases. Here again, however, the results at times are not good because it is used too strongly. The full-strength ointment should never be prescribed at first. If there is a great deal of maceration between the toes, with excessive perspiration, the ointment should not be used at all and the same formula prescribed as a lotion for its drying effect. Begin with 25 per cent strength ointment and increase if necessary, depending on the toleration of the skin. The feet should be washed at least once a day.

Whitfield's Ointment (full strength)

R̄	Ac. salicylic.....	5ss	2 0
	Ac. benzoic.....	5j	4 0
	Lanolin.....	3ss	15.0
	Petrolati.....	q. s. ad 3j	30.0

Sig.—Apply between the toes at night.

In the form of a lotion (full strength) it is prescribed as follows:

R̄	Ac. salicylic.....	5j	4.0
	Ac. benzoic.....	5ij	8.0
	Sp. vini rect.....	q. s. ad 3ij	60.0

Sig.—Apply between the toes night and morning.

A powder may be used during the day, dusted all over the feet:

R	Ac. salicylic.....	gr. xv- $\bar{5}$ ss	1.0-2.0
	Thymol.....	gr. xv-xx	1.0-1.3
	Amyli (rice).....	$\bar{5}$ ij	8.0
	Zinc stearate.....	$\bar{5}$ ss	15.0
	Talc.....	q. s. ad $\bar{5}$ ij	60.0

Sig.—Apply to feet in the morning.

There are several other lotions that may be prescribed if the various modifications of Whitfield's formula do not help.

R	Thymol.....	$\bar{5}$ ss-j	2.0-4.0
	Ol. cinnamon.....	gtt. xv- $\bar{5}$ ss	1.0-4.0
	Sp. vini rect.....	q. s. ad $\bar{5}$ ij	60.0
R	Thymol.....	gr. xv- $\bar{5}$ ss	1.0-2.0
	Camphor.....	$\bar{5}$ ss-j	2.0-4.0
	Ac. salicylic.....	$\bar{5}$ ss-j	15.0-30.0
	Sp. vini rect.....	q. s. ad $\bar{5}$ ij	60.0

Iodine may be used, either in a 5 to 10 per cent ointment, or the tincture, 5 to 10 per cent in alcohol. However, iodine may be very irritating and one should be careful with it.

If there is acute inflammation of the skin with exudation between and on the toes and feet, do not begin with any of these remedies but treat it first as an eczema. That is, start off with wet dressings of Burow's solution (1:4), or potassium permanganate solution (1:2000). A very valuable remedy in this stage is medicinal gentian violet (2 to 3 per cent) in aqueous or alcoholic solution. The alcoholic solution may be more efficacious but on an exuding surface burns and is apt to be irritating. After the acute stage has quieted down the fungicidal ointments and lotions are used.

The next most common type of dermatophytosis is the vesicular form, with or without interdigital involvement. In the acute stage, here again do not start with strong fungicidal remedies. First use wet dressings or soaks as given above. If new lesions continue to appear in spite of treatment, try silver nitrate solution ($\frac{1}{4}$ to $\frac{1}{2}$ per cent) as a soak or wet dressing. When the vesicles have opened and are drying up, gentian violet or the other lotions are begun. In the subacute stage do not use ointments but pastes, in which the fungicidal remedies may be incorporated.

The least common variety is the hyperkeratotic form, which may also be associated with infection between the toes.

Here one must use strong ointments, and Whitfield's is as good as any. The rough, thickened skin has to be peeled off, and for this purpose salicylic acid is very valuable. On the soles of the feet, salicylic acid plasters (10 to 25 per cent) may be applied with good results, being careful to cover the involved skin only and not to irritate normal skin.

Any of these types of dermatophytosis may have an accompanying eruption, the so-called "dermatophytides," which is even a greater problem. Generally this occurs on the hands as a discrete, vesicular eruption or an eczema. However, it may extend up the arms and legs, and may be more or less widespread.

The dermatophytides are supposed to be an allergic or toxic response to the fungi in the original focus of infection. It is a good plan never to treat this toxic eruption with fungicidal remedies, but as an eczema. If you find any evidence of infection between the toes treat that with Whitfield's ointment or the other remedies but use the various soothing preparations on the secondary dermatophytide.

For years "trichophytin" and other fungous extracts have been used in the treatment of these stubborn, recurrent eruptions, but I must say with disappointing results. However, although I do not recommend this as a routine procedure, they are worth trying in recalcitrant cases. As most people have a fungous infection on the feet, the intradermal test with these extracts is usually positive to a variable degree. In those who give a strongly positive reaction it may be of value to attempt desensitization with the extracts, but one must be careful of dosage and stop if there is a marked reaction or the eruption gets worse.

Recurrences in all forms of dermatophytosis are common. Therefore the question of prophylaxis is very important. The fungi may be harbored in stockings, house slippers, shoes, bath mats, bath tubs, etc. The person with "ringworm" of the feet should never go barefooted or have his bare feet in shoes or slippers. Women cannot boil silk stockings and so may reinfect themselves. A thin cotton sock, which may be boiled, can be worn underneath the stocking to prevent this. Rubber bathing slippers are not in themselves preventive because water gets into them. It is safer to wear cotton or lisle socks with

them. The bath tub should be washed out with a 2 per cent solution of sodium hypochlorite. This same solution, in 1 per cent strength, is valuable as a soak for the feet before and after the bath, and is being used in gymnasiums and golf clubs. The feet, especially between the toes, should be thoroughly dried after the bath, and the fungicidal powder prescribed above dusted on. In spite of all these precautions the condition may recur because of infection in the toe nails. Always inspect the nails and treat them if they look in the least abnormal. However, tinea of the nails is most difficult to eradicate and may require surgical removal. In stubborn and severe cases of dermatophytosis check up the patient generally and examine the urine. A lowered general resistance from some cause may be the factor in a persistent ringworm infection of the skin.

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THE MEULENGRACHT TREATMENT OF BLEEDING PEPTIC ULCER

THE Meulengracht treatment of bleeding peptic ulcer consists essentially of a program of liberal feeding, which is initiated immediately upon hospitalization of a patient for hematemesis and melena from ulcer. The diet is supplemented by the administration of iron compounds intended to assist in the regeneration of blood as well as a mixture designed to exert an antacid-antispasmodic effect. The purpose of this paper is to report one year of experience with this program. Since the chief merit of the Meulengracht regimen is alleged to consist in the reduction in the immediate mortality rather than in the ultimate cure of ulcer, this brief period suffices to an evaluation of this claim.

The original Meulengracht regimen was as follows:

"Puree diet. 6:00 a.m. Tea, bread and butter. 9:00 a.m. Oatmeal with milk, bread and butter. 1:00 p.m. Dinner. 3:00 p.m. Cocoa. 6:00 p.m. Bread and butter, sliced meats, cheese, etc., tea. All the bread given has been white bread. The dinner includes a great variety of dishes. The main dishes are, for example: meat balls, timbale, broiled chops, omelet, fish balls, vegetable gratin, meat gratin, fish gratin, etc., mashed potatoes and vegetable purees. In addition soup of vegetables, tapioca pudding, etc. As to the quantity of meals, the patients have been allowed to take as much as they cared for. In some cases where the patients had lost a large amount of blood, they were given one or two transfusions, soon after admission. . . . (The medication consists of). 1) Sodii bicarbonatis, Magnesii subcarbonatis aa 15 grams, Extr. hyoscyami 2.0 grams. Of this one teaspoonful three times a day. 2) Tabl. ferrosi lactatis, 0.50 grams, three times a day."

This program was modified in our cases in the following manner:

Breakfast: cream of wheat, farina, puffed rice or strained oatmeal. Eggs, any style, raw bacon, white bread toast with the crust removed, tea or coffee with milk or cream and sugar.

Lunch: baked macaroni and cheese or buttered spaghetti, or creamed eggs on toast, egg salad sandwiches (mixture of egg and mayonnaise only), cream cheese and jelly sandwiches, steamed rice, white bread, butter, custards, jello, plain or flavored corn starch pudding, coffee, tea, milk and sugar.

Dinner: cream soups, baked, boiled or mashed potatoes, pureed vegetables (spinach, peas, carrots), white meat of chicken, scraped beef, lamb chops, roast lamb, white fish, white bread, butter, desserts and beverages as above.

A typical diet for one day is shown in the following example:

Breakfast:

Farina.....	60 Gm. or 1 cup
Sugar.....	10 Gm. or 1 tsp.
Milk.....	180 Gm. or $\frac{3}{4}$ cup
Eggs.....	100 Gm. or 2
Bacon.....	40 Gm. or 2 strips
Toast.....	60 Gm. or 2 slices
Butter.....	10 Gm. or 2 tsp.
Coffee.....	1 cup
Cream.....	50 Gm. or $\frac{1}{4}$ cup
Sugar.....	10 Gm. or 1 tsp.

Lunch:

Baked macaroni and cheese

Macaroni.....	40 Gm. or 1 cup
Cheese.....	20 Gm. or 1" cube
Cream sauce	
Butter.....	10 Gm. or 2 tsp.
Flour.....	5 Gm. or 1 tsp.
Milk.....	120 Gm. or $\frac{1}{2}$ cup
Bread.....	60 Gm. or 2 slices
Butter.....	10 Gm. or 2 tsp.
Custard	
Egg.....	50 Gm. or 1
Milk.....	120 Gm. or 4 oz.
Vanilla	
Nutmeg	
Sugar.....	5 Gm. or $\frac{1}{2}$ tsp.

Tea	
Milk.....	60 Gm. or $\frac{1}{4}$ cup
Sugar.....	10 Gm. or 1 tsp.

Dinner:

Creamed soup	240 Gm. or 1 cup
Milk.....	5 Gm. or 1 tsp.
Flour.....	10 Gm. or 2 tsp.
Butter.....	50 Gm. or $\frac{1}{4}$ cup
Puree carrots.....	100 Gm. or $\frac{1}{2}$ cup
Puree spinach.....	90 Gm. or 3 oz.
Meat.....	120 Gm. or 1 med.
Potato.....	60 Gm. or 2 slices
Bread.....	10 Gm. or 2 tsp.
Butter.....	1 cup
Tea.....	60 Gm. or $\frac{1}{4}$ cup
Milk.....	10 Gm. or 1 tsp.
Sugar.....	1 portion
Jello.....	

The total protein in this example is 111 Gm., fat 161, carbohydrate 317; the total calories amount to 3200, this actually representing 900 more calories than the specimen diets of Meulengracht. Patients are also allowed a mid-morning and mid-afternoon feeding of cocoa, stewed fruit, etc., if they desire it. As a rule it is not requested. It is important to note that the above schema is merely a suggestion and the dietary program is not intended to be a weighed and measured regimen.

The medication has also been altered. We have employed ferrous sulfate in place of "lactatis ferrosi." In some cases this is supplemented during the second and third weeks by sodium cacodylate or a similar arsenical compound. Likewise we have not employed the antacid mixture advocated by Meulengracht. Colloidal aluminum hydroxide in doses of 2 drachms before meals or between feedings has been prescribed in some cases. Recently no antacid has been given unless the patient presented definite indications for its use.

Before reviewing the results obtained from this program, brief reference should be made to observations which suggest the advisability of liberal feeding: (1) often the more faithfully the inanition therapy is followed, the weaker patients become and the higher the mortality; (2) ambulatory patients who do not realize the significance of "tarry" stools and therefore do not alter their diets, according to Lenhartz, often have a very favorable course; (3) the appropriateness of inanition, of limitation of fluids, salts, calories, and vitamins is subject to question in the management of posthemorrhagic shock and posthemorrhagic anemia; (4) it is doubtful whether emptiness of the stomach in the presence of unneutralized acid is suitable either for hemostasis or for healing; (5) it is hardly conceivable that an insufficient diet will promote regenerative

processes. On the contrary there is reason to believe that a high vitamin C diet tends to prevent oozing of blood in the late posthemorrhagic period; that an abundant supply of carbohydrates protects the liver by avoiding acidosis and that acidosis retards wound healing; that experimental histamine hypersecretion or the administration of hydrochloric acid in dogs produces a pyloric gastritis in the empty stomach but not in animals given a liberal diet; that anemic dogs regenerate blood much more rapidly on diets containing meats and liver than when they are fasting or fed upon carbohydrates and milk.

However, the crucial question is whether or not the immediate mortality rate is reduced by liberal feeding. As a matter of fact, considerable uncertainty exists upon the true mortality rate from this cause and adherents of almost any therapeutic program can find comfort in published statistical reports which indicate mortality rates varying from 3 to 58 per cent. Most of these reports range from 7 to 15 per cent and the average reported mortality rate is 11.4 per cent. Moreover this percentage grossly misrepresents the real situation under the old program because it neglects milder and non-hospitalized patients; presumably the actual rate under the older conservative programs is below 7 per cent.

Working in a community in which the mortality rate from hemorrhage approximated 8 per cent, Meulengracht observed a reduction in the mortality to 1.3 per cent in a series of 368 consecutive cases. On the basis of 106 cases of hemorrhage treated by the Meulengracht program, Gram concluded that the death rate should not exceed 2 per cent under this mode of therapy. Recent medical literature contains numerous reports confirming this reduction in mortality under the Meulengracht program.

For the purpose of comparison the last 30 admissions for hemorrhage from peptic ulcer, treated by the old regimen, may be contrasted with the first 30 treated by the writers with the Meulengracht program. In the first group there were six deaths; among the 24 survivors 1 had a recurrence of hemorrhage and another developed perforation and required immediate surgical intervention. This mortality rate of 20 per cent among patients entering with hemorrhage is not unusual among

the neglected cases which reach a large city hospital. In the second group, treated by the Meulengracht regimen, there have been no deaths. In 1 patient hemorrhage recurred three months after discharge, but recovery was prompt under the Meulengracht regimen. His ulcer is still demonstrable three months after his second discharge but he remains free from symptoms. One patient continues to have dyspepsia; he refuses to adhere to any dietary program, drinks heavily and smokes considerably. A third patient, a known syphilitic, complains of persistent weakness presumably associated with parenchymatous syphilis of the central nervous system which he will not allow to be treated. Finally one patient developed postprandial pain one week after discharge; he attributed this to an inability to secure an antacid. Colloidal aluminum hydroxide immediately gave relief and he still occasionally resorts to its use eight months after discharge from the hospital.

It cannot be asserted with any degree of confidence that this drastic reduction in the mortality rate is real. The literature reports that on the average 13.5 days elapsed between hemorrhage and death in patients treated by the old program. Except in one instance our deaths occurred within thirty-six hours and among young individuals with a brief history in whom the rapid evolution of their erosive process did not permit the development of an occluding arteritis; or, older individuals with a prolonged history of recurrent hemorrhage in whom arteriosclerosis probably prevented the rigid vessel from closing. Every clinician who has seen a gaping blood vessel fixed in the wall of a callous ulcer realizes that any conservative method of management sooner or later must end in disaster if it is routinely applied. One patient treated by the Meulengracht regimen entered in profound shock, the blood pressure amounting only to 60 mm. Hg systolic and 10 diastolic and the blood count revealing 1,100,000 erythrocytes. Although several of the cases were equally severe it cannot be said that all or even most of our earlier deaths could have been prevented by the liberal program. While we have employed the Meulengracht regimen in every patient for experimental purposes, we intend to revert to a program of individualized therapy for individual cases. However, it should be emphasized that all

writers who have employed the treatment have observed a reduction in the mortality rate:

In Copenhagen, the medical students relate a joke about the Meulengracht regimen. They say, "The treatment of hematemesis is now very simple. One simply tells the patient to wash the blood from his mouth and to eat beefsteak." Naturally the Meulengracht regimen represents a startling contrast to the methods in vogue in most hospitals. Except for Andersen, in America most institutions advocate three days of abstention from food followed by a graduated diet. The discomfort of the starvation period is circumvented in part by a continuous intravenous drip of 5 per cent glucose which minimizes dehydration and provides some sugar during the critical period. This raises the question of whether or not the stomach will tolerate feeding soon after hemorrhage. We encountered only one instance of gastric intolerance to feeding; but since this disappeared immediately after discontinuing the iron medication and without alteration of the diet it would seem that the food was not responsible. Rischel did not encounter a single instance of gastric intolerance necessitating interruption of the treatment in 198 cases managed by the Meulengracht program; moreover 175 were discharged free from dyspepsia. Others recovered from their hemorrhage but were unrelieved of gastric discomfort. Since dyspepsia often disappears spontaneously after hemorrhage we are not able to determine the rôle of feeding in this respect, although alkalies are much less often required for symptomatic relief. While dyspepsia may begin after hemorrhage treated by the old plan, this was not encountered under the new method. There appears to be unanimity among all workers that liberal feeding is not associated with gastric intolerance but rather with the early disappearance of dyspepsia.

Most patients entering the hospital during or immediately after hemorrhage are suffering from more or less severe shock. In practically all cases morphine is administered not simply to induce complete rest but to allay apprehension. Since it tends to splint the bowel and cause nausea and vomiting, its continued use is not desirable. The administration of barbiturates is preferable when prolonged sedation is required. However, sedation does not appear necessary over so long a period under

the Meulengracht regimen as under the starvation program. Patients in shock are placed in a recumbent position but as a rule the foot of the bed is not elevated. While the latter may assist cerebral circulation, it may accentuate stupor by decreasing the venous return to the heart.

Most gastro-enterologists advise against the overuse of transfusion, since severe reactions occur and the resultant injury may be more deleterious in some cases than any potential benefit. Moreover, narcotized patients tolerate shock and anemia better than alert individuals. The general rule of withholding transfusion until the hemoglobin reaches 30 per cent or the systolic blood pressure 90 mm. Hg seems to be a safe guide. However, in order to contrast our early and late series, all patients exhibiting shock were given one or more small transfusions none of which exceeded 150 cc. One patient presenting moderate shock continued to bleed under the Meulengracht program as evidenced by fresh hematemesis twelve and thirty-six hours after hospitalization. At this time he was transfused, and bleeding did not recur. Meulengracht finds it necessary to transfuse approximately 10 per cent of patients.

The occurrence of hyperazotemia is a well-attested phenomenon in posthemorrhagic states. It has been attributed to the anemia and the reduced protein content of the blood and it is well known that secondary shock is associated with marked destruction of the body proteins. We have not encountered it since the institution of the Meulengracht program, but it has been observed by others who do not transfuse freely. At any rate one should carefully balance the dangers of anemia, hypoproteinemia and posthemorrhagic shock against the dangers of rapid restoration of the original blood pressure level and transfusion reactions.

Since nausea and vomiting are usually abolished by the Meulengracht method, gastric lavage with warm water for removing these symptoms is unnecessary; in fact, the writers never attempted this procedure under the starvation program. Many clinicians advocate the use of cold or hot applications to the abdomen. Cold may chill an already shocked patient and the theoretical advantages of hot compresses seem to be outweighed by the necessity of disturbing the patient con-

stantly by their renewal. The writers have not employed any of the so-called "hemostatic agents" for the management of hemorrhage from peptic ulcer.

Schiødt made serial investigations of the blood count in patients under the inanition program as well as the Meulengracht regimen. Regeneration occurs much more rapidly under the latter. This was also observed in our series although older patients showed a slower response than the regeneration curves published by Schiødt. Nevertheless the convalescent period in all cases is considerably shortened by the Meulengracht regimen. It is practically impossible to keep the patients in bed for two weeks. This represents a considerable saving in hospital days since six weeks of hospitalization were not uncommon when graduated and measured diets were employed. The freedom from symptoms, the rapid return of strength, and ability to eat, the absence of irritability concerning too little and too monotonous diet are important factors in shortening a convalescent period and expediting return to work. Regardless of whether or not the mortality rate has been lowered there is little doubt that convalescence has been more rapid and pleasant under liberal feeding. Nothing can be said about ultimate results but it may be anticipated that they will approximate those obtained by other "smooth diets."

While the Meulengracht regimen has been advocated for the treatment of hematemesis and melena from a variety of sources, the writers are not especially sanguine over the results obtained in some groups of cases. For example, no great benefit followed its use in the posthemorrhagic phase of cirrhosis of the liver, although the diet has been administered soon after rupture of an esophageal varix. We have followed the blood counts in a small series of cases of inoperable carcinoma of the stomach and bowel and failed to see any improvement in this direction from the Meulengracht regimen.

It would appear that greater liberality in the diet is permissible in the management of bleeding peptic ulcer. There is suggestive evidence that liberality is associated with decreased mortality and shorter hospitalization. It should be emphasized again that the Meulengracht program consists in the quantitatively unlimited administration of qualitatively selected foods, rather than in a graduated measured diet.

This is supplemented by the administration of substances capable of assisting blood regeneration, especially iron compounds. Since serial gastric analyses in our cases showed considerable amounts of unneutralized acid present it seems advisable to employ antacids regularly although they are not necessary for symptomatic relief. The employment of antispasmodics, such as belladonna, has widespread popularity although their real value is unknown.

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CLINIC OF DR. WALTER A. BASTEDO

ST. LUKE'S HOSPITAL

THE TREATMENT OF CHRONIC DYSPEPSIA

CHRONIC dyspepsia is a layman's diagnosis. The term does not stand for any clinical entity. Yet there are many people whose stomachs give them more or less care throughout life. They cannot eat freely of various ordinary foods that other people eat, they may be distressed by fruits and fruit juices, they must avoid highly flavored food and spices, they cannot take candy and sweets, they may need to shun tea and coffee, and cocktails are taboo. Otherwise they risk distress, and dependence on the sodium bicarbonate bottle or other remedies for several days or weeks.

For most of the time these patients get along well enough if they are abstemious and careful. At least, they may have periods when they feel digestively well, and can indulge in forbidden foods and drinks. Yet the immunity from symptoms does not last, and from time to time, either as the result of indulgence, or for nervous reasons, or without any known reason, they have exacerbations, during which it is necessary for them to restrict the diet to the blandest types of food. These are the chronic dyspeptics.

To the physician a history like the above suggests a search for an assignable cause, such as gastritis, gastric atony, peptic ulcer, cholecystitis, colitis, chronic or recurring appendicitis, disease of the pelvic organs. As not infrequently the attack is accompanied by a state of nervousness, he may be satisfied that this is the cause. Or he may suspect an allergic reaction. Many of the patients come in one or other of the above categories; but, while the possibility of such a diagnosis must always be kept in mind, there are many for whose symptoms no definite cause is discovered. They complain of discomfort or pain in the stomach region, coming on soon after meals or

late in the intermeal period, or of irregular bowels, or of gas. Some feel better if they eat, others if they do not eat. Rarely do they have nausea or vomiting, but they may regurgitate acid into the throat. They all believe that they have "acid stomach."

TREATMENT

The differential diagnosis is not included in this talk, so we proceed to treatment. The primary considerations in treatment are diet, care of the bowels, and medicines to alleviate.

Diets.—In regard to these, prejudice and tradition are often the guides, rather than the knowledge that has been given us by experts. One physician irritates the stomach by a roughage diet ordered because of the bowels, another specifies a supposedly bland diet because of the stomach, while insisting on apricots, prunes and other cooked fruits. Some exclude the citrous fruits, or all fruits, or the starches, or milk, or eggs, or meats, without, to others, any obvious reason.

Most entertaining of all, perhaps, were it not tragic, is the order to exclude *red or dark meat*. Beef, the beef of old England, has been a mainstay of the healthy and aggressive races for centuries. Why then must all those who desire health nowadays be forbidden beef? The red meats are charged with containing a greater amount of extractive, chiefly creatine, the nucleins, and the xanthine bases which favor the production of uric acid. Yet over thirty years ago Offer and Rosenquist demonstrated that the purine content of light and dark meat was practically the same, and that there were greater differences in the percentages of nuclein and purine in pieces of meat taken from different parts of the same animal than were found on an average between chicken and beef. Beef, lamb, chicken, turkey and veal are about equal producers of extractive. The flesh of fish produces only half or two thirds as much. These findings have been corroborated by Hall, Hutchinson, Gaultier, Strauss and other food chemists. The only significant differences between light and dark meat are in the amounts of blood and connective tissue present. The latter relates to toughness and not to food value, and is partly dispelled by adequate cooking.

How Must the Diet Be Managed?—In all conditions that suggest local hyperirritability I favor a diet that is bland, that

is, of comparatively smooth and soft character and free from obvious roughage. Complete blandness, if attainable, is not desirable for any great length of time. Likewise, a one-sided diet, or one inadequate in amount, must not be continued too long, therefore, as soon as possible, the diet should be made to include ample quantities of the various classes of foods. Till the patient can take these with apparent impunity he may be considered only temporarily improved.

It is not necessary to have an individual diet for every namable condition, for the diet that is suitable for one condition of hyperirritability is suitable for others. Even such a specific diet as that for ulcer is sometimes good for other hyperirritable conditions than ulcer. In some instances, there may be good reasons for the exclusion for a time of all flesh, or of eggs, or of milk, or of fruit. But these are good foods and should be returned to the diet as soon as feasible.

If the physician has 3 or 4 graded diets he may begin with the lowest during an acute exacerbation, or with number 2, 3, etc., according to the severity of the symptoms. I therefore suggest several basal diets, of which 1 and 2 are for bed patients with severe exacerbations, 4 and 5 for ambulatory or office patients, and 3 for either.

Diet 1.—Peptonized milk, 3 ounces every hour, the amount to be increased as soon as the stomach is tolerant. Or one may use albumin or barley water. This is the early stage of an ulcer diet.

Diet 2.—Peptonized or raw milk, with the addition of 1 or 2 eggs to the quart, 4 to 6 ounces every hour, with the substitution once or twice a day of orange juice, orange or lemon albumin water, milk toast, tea and toast, junket or custard. This is a later stage of ulcer diet.

Diet 3.—Cream of wheat or strained oatmeal gruel. White bread, toast, zwieback or plain crackers, with butter. Milk. Milk toast. Eggs, soft boiled, soft poached or raw. A small helping of strained purée or cream soup of green peas, green beans, corn, celery or potatoes. Beef tea or bouillon. Baked potato with butter. Custard, farina, cornstarch, plain rice pudding, junket, vanilla ice cream. Cocoa, weak tea, lemonade, orange or lemon albumin water, beef juice. One glass of orange, grapefruit or tomato juice each day, whichever is best

borne by the stomach. Salt as desired, but within reason, and no pepper or other condiment.

Diet 4.—One might call this the “hyperacidity diet,” a suitable beginning one for many office patients. At first it may be wise to strain all vegetables except the starchy ones.

Farina, cream of wheat, hominy, boiled or puffed rice and corn or rice flakes. White bread, toast, zwieback, bread rolls, plain soda crackers. Butter, cream, milk, peanut butter. Sugar, just enough for flavoring purposes. Eggs, soft boiled, soft poached or raw. Strained purée or cream soups of peas, beans, lentils, corn, celery, potatoes, avoiding greasiness and pepper. Fresh fish, lamb chop, roast lamb, beef steak, tender roast beef, chicken, turkey, squab, brain, sweetbread, calf’s liver, rejecting fat and gristle. Potatoes (baked, boiled or creamed), spaghetti or macaroni (plain or creamed), rice, noodles, peas, lima beans, string beans if tender and not stringy, carrots, squash, tender beets, Swiss chard, beet tops. Custard, cornstarch, blanc mange, rice pudding, tapioca, sago, junket, other milk and cereal desserts without much sweetness, vanilla ice cream, plain cake. Orange, grapefruit or tomato juice, strained apple sauce. Cocoa, weak tea, milk, vichy, lemonade, orangeade. Salt as desired.

Diet 5.—This is a diet that may be continued indefinitely. As it is very comprehensive the physician should cross off some things that cannot yet be allowed. It includes:

Any cereal, except those with added bran.

White bread, whole wheat bread if made of fine flour, toast, zwieback, bread rolls, plain soda crackers, light corn bread.

Butter, peanut butter, cream, milk. Sugar, just enough for flavoring.

Eggs soft boiled, soft poached, scrambled, raw or in the form of a light omelet.

Purée or cream soups of peas, beans, lentils, corn, celery, potatoes, asparagus, spinach. Clear soups, broth or bouillon. Oyster stew.

Fresh fish, lamb chop, roast lamb, beef steak, tender roast beef, veal, duck, chicken, turkey, squab, brain, sweetbread, kidney, liver, stewed oysters or clams. Have all meat free from fat or gristle and cooked by roasting, boiling or broiling. A small helping of lean bacon may be allowed as flavoring.

Potatoes (baked, boiled, mashed or creamed), plain or creamed spaghetti or macaroni, rice, noodles, peas, lima beans, tender string beans, plain baked beans, carrots, squash, tender beets, spinach, Swiss chard, beet tops, asparagus, stewed celery, stewed tomatoes (and, perhaps, parsnips, artichoke, corn, fresh mushrooms, sweet potato, eggplant).

Lettuce or endive with peeled raw tomato, and lemon juice, oil and salt.

Custard, farina, cornstarch, blanc mange, rice pudding, tapioca, sago, junket, other milk and cereal desserts without much sweetness, ice cream, plain cake, honey, cottage or cream cheese (perhaps American or Swiss cheese).

Cooked or canned fruits except berries—such as apple, pear, peach, prune, banana baked in the skin. Orange, grapefruit, tomato, or other fruit juice. Raw apple, pear, peach, orange, grapefruit, very ripe banana, melon. (Skins of fruit and orange fiber should not be swallowed in the first stages of this diet.)

Cocoa, weak tea or coffee with sugar and milk or cream, Kaffee Hag, Sanka, Postum, milk, vichy, lemonade, orangeade. Salt as desired.

Avoid particularly: excess of salt, pepper, mustard and similar condiments. Highly flavored foods and those that are fried, acid, spicy, salty or very sweet. Rich cream, bran, figs, pineapple, berries. Pickles, olives, radishes, raw onions, cucumber, nuts. Coarse breads and crackers such as graham or bran. Tongue, corned beef, spiced or dried beef, goose, pork, sausage, ham. Crab, lobster, mackerel, caviar, anchovies, canned or salt fish. Coarse, stringy or highly flavored vegetables, such as turnips, broccoli, kohlrabi, cabbage, Brussels sprouts, cauliflower, oyster-plant, onions. Pastry, pie, rich cake, hot bread or biscuits, griddle cakes. Strong coffee, alcoholic drinks, gingerale, soda water, soured or fermented milks such as buttermilk, zoolak and acidophilus milk.

It may be desirable to exclude for a time meat and eggs because of intestinal putrefaction, sugar and the more starchy vegetables on account of fermentation, fruit juices or fruit because of irritation. milk because of an idiosyncrasy against it, or some special foods because of an allergic reaction. If com-

fort is not obtained, all nonstarchy vegetables should be strained, or a lower diet adopted.

As we are dealing only with the nonspecific cases of dyspepsia, this talk does not include the special diets for ulcer, cholecystitis, etc.

The Bowels.—Whatever else is done, these must be regulated. If the stomach or colon is hyperirritable one cannot utilize fruits and coarse vegetables. In this case, perhaps one of the many available bulk-producing and softening remedies will suffice, such as mineral oil, agar, bassorin or hulled psyllium. But sometimes these are not acceptable to the stomach or are unsuccessful in producing a proper stool. Thus it may be necessary for a time to employ magnesia, milk of magnesia, aloin, cascara, senna, rhubarb or phenolphthalein. The drastic cathartics, being irritant to both stomach and bowels, are not used.

Magnesia may be included with other antacids in a powder. Milk of magnesia taken at bedtime, in amounts small enough to avoid liquid stools, serves also as a bedtime antacid. Phenolphthalein is prone to keep the movements loose, hence the dose must be kept low. Not infrequently it has been found to produce a disagreeable rash. For continued use in the obstinately constipated, where colonic hyperirritability does not predominate, aloin, cascara, senna and rhubarb have proved of great value.

Many of the patients can regulate the bowels by taking a laxative two or three times a week; but, as a rule, better ultimate results are obtained by giving the drug every day, no matter how small the amount required. When the patients are able to eat fruits and vegetables in adequate quantities they may not need a laxative further, or may get along with a dose occasionally, perhaps once a week.

Alleviating Remedies.—The chief of these are the so-called *antacids*. Of long use are sodium bicarbonate, calcium carbonate, magnesium oxide (light and heavy) and magnesium carbonate.

In neutralizing power 1 Gm. of magnesium oxide is equivalent to 2.5 of magnesium carbonate, 3 of calcium carbonate, 4 of sodium bicarbonate and 21 cc. of milk of magnesia. These amounts will neutralize 18 cc. of diluted hydrochloric acid, or

600 cc. of gastric contents containing 0.3 per cent of hydrochloric acid. Thus these remedies would seem to be very potent as antacids. But their relative values as alleviating remedies are not to be measured solely by their power to neutralize acids. They have other actions that are important.

In any event they are only symptomatic remedies of brief action, and the time for their administration is when the distress appears, or, if it recurs at a regular time each day, just before that time. If given at the wrong time, as after meals when the discomfort comes an hour or two before meals, the remedy is futile or harmful. As a rule alkalis should not be given in large quantities immediately after meals, for they destroy all pepsin and stop digestion. Following this stage, when the stomach recovers and renews its secretion of gastric juice, it sometimes responds by a decided hypersecretion to the need to digest the food that it contains. At times, however, a small dose after meals, especially with the addition of a carminative, will cause the expulsion of gas and promote the aftermeal comfort.

In most patients the distress is associated with the empty time of the stomach, or what would normally be the empty time, *i. e.*, late in the intermeal period. The food has disappeared, but there is plenty of free acid in the stomach, and relief is obtained by an antacid or by simple food such as milk, taken at the time.

But in some there is pylorospasm with epigastric distention, from which relief is sought by loosening the clothing. This may be accompanied by the same empty gone feeling late after the meal, and some of these patients have even obtained relief by taking food, just as in the acid stomach truly empty of food. But on passing a stomach tube in these patients at 5 o'clock or thereabouts, even after they have obtained relief from milk or other food, we have found much of the luncheon still present, usually very acid, fermenting, and containing chunks of unmasticated food. The stomach tube has revealed the diagnosis. Such a condition is overcome by better care in mastication, less hurried eating and a better arrangement of the menu, with perhaps late afternoon lavage for a few days, or antacid medication administered late in the intermeal period.

In spite of sundry objections to its use, recently brought forward, *sodium bicarbonate* continues to be the antacid of choice of a large number of physicians, who, however, frequently add magnesia and chalk as supplements to it. The reasons for its apparent superiority are: (1) it is the physiologic alkali of the body; (2) it is the only one of these antacids that is soluble, and in dilute solution it is soothing to irritated mucous membranes; (3) in the presence of acid it gives off the carminative and soothing carbon dioxide, and leaves a weak and nonirritant solution of sodium chloride; (4) it has a special power to relax the pylorus and possibly also the cardia (Spencer, Rehfuß *et al.*, Cannon); (5) it stimulates the motor function of the stomach; (6) being in solution it may help to dissolve mucus. *It should never be given continuously in large enough quantities to render the urine persistently alkaline.* Magnesia and magnesium carbonate are insoluble, but in the stomach form magnesium chloride. If given directly after meals, this checks the salivary digestion that normally continues for half an hour after meals (Hawk). Calcium carbonate is insoluble, and in the stomach forms the very irritating calcium chloride. The magnesium salts and calcium carbonate are not systemic alkalizers.

Antacid Substitutes.—Owing to the possibility of systemic overalkalinization by sodium bicarbonate, remedies have been introduced that purport to reduce the acidity of the gastric contents without alkalizing systemically. Such are the dibasic and tribasic phosphates of calcium, the dibasic and tribasic phosphates of magnesium, colloidal aluminum hydroxide, aluminum silicate and magnesium trisilicate. Any of these may be employed in the same dosage as sodium bicarbonate.

Bismuth salts are not antacids, but they coat the membrane of the stomach and act as local protectives and demulcents.

Carminatives.—Though spices in the food are prone to enhance the symptoms, a mild carminative at the proper time may lessen them. This is especially true if it is given with an antacid. Aromatic spirit of ammonia or spirit of peppermint may be employed, with the addition of sodium bicarbonate; or oil of peppermint or cinnamon as an addition to antacid powders. A favorite carminative of the author is: R Tinct. lavand. comp., Spt. ammon. aromat., Spt. chloroformi, āā 30

cc. (1 ounce). M. et Sig. One teaspoonful in hot water, for gas (with or without the addition of sodium bicarbonate).

Atropine and belladonna have been much prescribed on the theory that they lessen pyloric spasm and the acid secretion of the stomach. But in the small doses permissible for administration to humans they do neither of these things. Very large hypodermic doses, enough to dry the throat, dilate the pupils, quicken the heart rate and affect the brain, may have an effect. But this effect is neither to relax the pylorus nor to lower the relative acidity. On the contrary, they tend to *increase* the degree of acidity by lessening the mucus and fluid of the gastric juice without lessening the total amount of acid secreted. (See author's article, "The Value of Atropine and Belladonna in Stomach Disorders," Jour. Amer. Med. Assoc., Jan. 11, 1936.)

Illustrative Prescriptions.—1. Sodium bicarbonate, or one of the nonalkalinizing antacids, 2 Gm. (30 grains), with a full glass of water on arising and at 11, 5 and bedtime (or whatever times may be selected).

2. A long-time, slightly laxative favorite is: \mathcal{R} Magnes. oxid., Calcii carbonat., Sodii bicarb., $\bar{a}\bar{a}$ 15 Gm. ($\frac{1}{2}$ ounce), Ol. menth. pip. 0.7 cc. (10 minims). M. et Sig. Half a level teaspoonful on arising, etc., as above. The proportions of these ingredients may be changed according to need.

3. Bismuth subcarbonate or subnitrate, 1.3 Gm. (20 grains), with water, after the morning and evening meals, or shortly before the meal.

4. \mathcal{R} Bismuthi subcarb., Sodii bicarb., Magnes. oxid., $\bar{a}\bar{a}$ 15 Gm. ($\frac{1}{2}$ ounce), Ol. menth. pip. 0.7 cc. (10 minims). M. et ft. chart. no. xx. Sig. One with water at 10, 4 and 9 (or whatever times are adjudged best). Magnesium oxide is a light fluffy powder, so many prefer the heavy oxide (magnesium oxidum ponderosum), which is more dense, though it acts more slowly as a neutralizer.

5. \mathcal{R} Sodii bicarb. 12 Gm. (3 drachms), Fluidext. cascarae 8 cc. (2 drachms). Mist. rhei comp., N. F., q. s. ad 120 cc. (4 ounces). M. et Sig. A dessertspoonful with a glass of water one hour before luncheon and dinner and at bedtime. For many years we have prescribed this mixture with varying amounts of the ingredients, and have frequently seen a gradual

lessening of its need till it was dispensed with altogether or taken only occasionally.

6. For laxatives, instead of the preceding, a pill of extract of cascara 0.3 Gm. (5 grains) or of aloin 0.012 Gm. ($\frac{1}{8}$ grain), or the aromatic fluidextract of cascara or the fluidextract of senna 4 cc. (1 drachm), may be given every night or occasionally. Or the remedies may be combined, as in \mathcal{R} Fluidext. sennae, Fluidext. cascarae aromat., Syr. rhei aromat., āā 30 cc. (1 ounce). M. et Sig. Half to 1 teaspoonful at bedtime. Senna is a good and successful home remedy, a few of the leaves being chewed at bedtime, or 2 ounces made into a pint of infusion, and a tablespoonful or 2 taken as the dose, with or without the addition of sodium bicarbonate. The mixtures of figs, prunes, dates, etc., with senna add nothing except a little harsh roughage to the senna action and are scarcely to be recommended.

Achlorhydria.—This not uncommon condition may be associated with gastric distress. It requires different treatment from that for hyperacidity. As the swallowed food is not diluted as usual by gastric juice, the contents are small in volume. Starch digestion is unusually prolonged. The stomach empties its contents very rapidly into the intestines, with resultant hungry or empty feeling two or three hours after meals. The swallowed bacteria are not destroyed as they are in normally or highly acid contents. Protein foods are more likely to putrefy in the intestines. The bowels may be overstimulated.

The swallowing of germs should be lessened by extra care of the teeth and mouth and by avoiding raw foods that cannot be peeled or properly cleansed, such as berries, celery and lettuce. But the raw foods, butter, cheese, milk and buttermilk may be permitted. The milk may properly be pasteurized. Fine disintegration of the food, by mastication or otherwise, is necessary.

Diluted hydrochloric acid may do these patients much good. But, owing to the sensitiveness of the throat, it cannot be administered in a strength to correspond with that of the gastric juice or high enough to activate pepsin or to have an antiseptic value, therefore it is not true replacement treatment. Yet it dilutes the gastric contents, and frequently appears to check flatulency and diarrhea and to promote comfort. The strong-

est acid that can be borne by the throat is given. For most people this is 4 cc. (1 drachm) of diluted hydrochloric acid in a glass of water, but some can swallow double this strength. It should be taken through a glass tube or straw to protect the teeth, and during or at the end of a meal. The solids, glutamic acid hydrochloride and acidulin, of either of which 1 capsule gives the acidity of 0.7 cc. (10 minims) of diluted hydrochloric acid, may be employed, but I have not found them satisfactory.

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SULFANILAMIDE IN THE TREATMENT OF ACUTE INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

THE story of sulfanilamide has been so thoroughly covered in numerous articles that it would be a waste of time to refer to the history of its development or to the details of its chemical composition. In this short paper, we shall confine ourselves mainly to the experience of the meningitis division of the health department.

At present, little is known in regard to the value of sulfanilamide in virus infections of the central nervous system. A certain amount of experimental work has been done which would indicate that it is of no value in poliomyelitis and in the St. Louis type of encephalitis. Rosenthal¹ has shown that prontosil possesses protective action in mice against the infection with the virus of lymphocytic choriomeningitis. It would be difficult to evaluate this clinically, since most of these patients recover promptly without any specific treatment. Holden in a preliminary experiment could find no evidence of any protection in rabbits treated with prontosil after infection with rather large doses of a neurotropic herpetic-like virus.

We have used sulfanilamide mainly in various types of meningitis. The results obtained clinically did not necessarily parallel the experimental work. For instance, in infections in animals, sulfanilamide seemed about as effective against the pneumococcus as against the hemolytic streptococcus or the meningococcus. In man, however, sulfanilamide is far less

effective in pneumococcic than in hemolytic streptococcic meningitis. Likewise, Povitzky² has shown that experimentally a combination of prontosil and specific serum protects quite effectively mice infected with fatal doses of the influenza bacilli. Using the same treatment in meningitis due to *Bacillus influenzae*, the results have been disappointing.

It should be noted that Branham and Rosenthal³ have demonstrated that a combination of specific serum and sulfanilamide was more effective than either agent alone in experimental infections with the meningococcus and the pneumococcus.

Sulfanilamide and its various derivatives have been used too short a time to admit of definite conclusions in regard to the optimum dosage and the best methods of administration. The preparations that we have used are prontosil intramuscularly, prontylin orally and at times an 0.8 per cent solution of prontylin crystals intraspinally. It is our impression that it is not necessary to use the large doses advocated by certain workers. As a rule we have given 5 cc. or less of the prontosil every four hours to younger children and 10 cc. every four hours to older children and adults. In addition, from 5 to 15 grains of prontylin have been given every six hours. We have felt that the use of the combination was preferable to either agent alone. With evidence of definite clinical improvement, the prontosil was usually discontinued but the prontylin was continued for a variable period.

We do not feel sure at present that there is any advantage in administering the sulfanilamide intraspinally. Indeed most of our recovered cases were not treated in this manner. Marshall, Emerson *et al.*⁴ have shown that there is a high concentration of sulfanilamide in the spinal fluid following oral administration. However, the 0.8 per cent sulfanilamide solution is nonirritating to the meninges and can do no harm. There may also be an advantage from a mechanical point of view in replacing a certain amount of the spinal fluid withdrawn. It has been stated by ourselves and others that prontosil should not be used either intravenously or intraspinally. There is no reason for the use of prontosil intravenously. Recently we have had reports of favorable results following the use of prontosil intraspinally. We have tried it ourselves in a few in-

stances with indefinite results but certainly with no serious reactions. The pH in prontosil is at present 6.8, which is compatible with its intraspinal use. We shall continue to investigate this manner of using prontosil.

There has been considerable discussion in regard to the toxicity of sulfanilamide. We have not observed such effects in any alarming degree. We realize of course that an occasional patient may be unduly sensitive to this as to any other chemical. As a result of hypersensitivity fairly severe reactions may occasionally occur, particularly agranulocytosis or hemolytic anemia. The milder reactions are rather common and do not contraindicate the continuation of the drug. Dyspnea which is due to acidosis can usually be prevented by the administration of alkalis. If the patient already has marked anemia or cyanosis or impairment of renal functions the drug should be used with caution. It is necessary to make repeated blood counts during the period of treatment.

We have used sulfanilamide in 23 cases that we have grouped as miscellaneous. In 3 instances, the patients presented a classical clinical picture of meningococcemia and they recovered promptly following the use of sulfanilamide although the blood cultures were negative. A fourth case with clinical evidence of meningococcemia and meningitis recovered with the use of this chemical, but later developed hydrocephalus and pneumonia and died. One patient recovered from hemolytic streptococcal septicemia. Another patient had a meningitis following scarlet fever and mastoiditis, which was operated. Gram-positive organisms were found in the smear, but the culture was negative. This patient recovered with the use of sulfanilamide and convalescent scarlet fever serum. In 1 instance, the patient had a mastoiditis and brain abscess due to the hemolytic streptococcus. Recovery followed the operation and the use of sulfanilamide. In 6 cases of meningitis where there was some question about the causative organism, recovery took place. The other cases do not warrant discussion with one exception, which was a brain abscess due to the influenza bacillus. This patient died.

There were three patients with meningitis with mixed infections. One of these had multiple brain abscesses as well. These three cases ended fatally.

Three patients with staphylococcic meningitis were treated. One patient, a baby twenty-four days old, recovered.

Ten patients with meningitis due to *Bacillus influenzae* received sulfanilamide in conjunction with the specific serum. There was only one recovery.

One patient developed meningitis due to the Friedländer bacillus eighteen days after the administration of spinal anesthesia for a bladder operation. It seemed to us unlikely that the spinal anesthesia was a factor. This patient was treated with sulfanilamide and also with phage. He improved for a time but eventually died of a spinal epidural abscess.

Three cases of meningitis due to a nonhemolytic streptococcus, two of which were definitely *Streptococcus viridans*, received sulfanilamide. One of these, definitely of the *viridans* variety, recovered.

Our results with sulfanilamide and specific serum in meningococcic meningitis to date have not been favorable statistically. The number of cases, 18, has been too small, however, to make statistics of much value. Of these 18 cases, 13 have recovered. One of these received sulfanilamide only. In the 5 fatal cases, there were certain extenuating circumstances. In one instance, the patient was only six weeks old. It is well known that meningitis is highly fatal in young infants. In another instance, the treatment was delayed for more than two weeks.

The case fatality in this group is much higher than our average. We have learned from experience, however, that a large series of cases must be considered for significant statistical results.

It has been our clinical impression, however, that in some instances where the patient has been critically ill, the recovery has been more rapid with the combination of sulfanilamide and serum than we should have expected with serum alone. At present it is our opinion that sulfanilamide may very well replace the use of serum intravenously in cases of meningococcemia with or without a meningitis. Schwentker, Gelman and Long⁵ and others have reported excellent results using sulfanilamide but only with small groups of cases.

We have used sulfanilamide in 25 cases of pneumococcic meningitis. Only 4 of these patients recovered. These were

caused by types 31, 29, 4 and 13, respectively. No serum was available. In 2 instances, the meningitis developed within forty-eight hours after an operation, in the 1 case a tonsillectomy and exenteration of the right ethmoid and in the other, submucous and turbinate resections. It is probable that in these cases, the primary foci were adequately drained. In the third instance, the meningitis followed a bilateral otitis media. A bilateral mastoidectomy was performed before the meningitis had developed. In the fourth, the focus was not definitely located although the presence of an ethmoiditis was suspected. Previously we had had a case fatality of 100 per cent.

Among the 21 fatal cases, there was a great variety of types of pneumococci with a slight preponderance of types 1 and 3. Most of these cases were associated with upper respiratory, sinus or otitic infection, or pneumonia. It is quite likely that in many instances an upper respiratory infection was associated with an undiagnosed sinusitis. In most of the cases it was impossible to diagnose during life the focal infection with sufficient definiteness to warrant an operation. It has seemed to us that the failure to remove the focus of infection may have been an important factor in the unfavorable results.

The most striking results by far have been obtained in the treatment of hemolytic streptococcic meningitis. During a period of more than twenty-six years, we had seen 274 cases of various kinds of streptococcic meningitis, most of which were of the hemolytic type. There were only 15 recoveries, 9 of which were definitely of the hemolytic variety. In a tenth recovery, there was a mixed infection of the hemolytic streptococcus and the meningococcus. Three of these recoveries were in patients in whom the meningitis developed following scarlet fever. In two instances, the antiscarlatinal serum was used and in the third, large amounts of convalescent serum and a small amount of prontosil and prontosil.

Since the beginning of 1937, we have treated 19 cases of hemolytic streptococcic meningitis, with 14 recoveries and 5 deaths. The details of these cases are shown in the Tabulation.

It will be noted that of the 5 fatal cases, sulfanilamide was used less than twelve hours in 2 instances and less than

TABULATION
CASES OF MENINGITIS DUE TO THE HEMOLYTIC STREPTOCOCCUS

Case.	Sex.	Age, years.	Primary source of infection.	Treatment.	Result.	Remarks.
1	F.	21	Right maxillary sinusitis. Right otitis with mastoiditis.	Drainage antrum; mastoidectomy, spinal drainage, sulfanilamide, convalescent scarlet fever serum.	Recovered.	Only a small amount of serum was given.
2	F.	7	Left otitis with mastoiditis.	Mastoidectomy, spinal drainage, sulfanilamide.	Recovered.	
3	M.	5½	Left otitis.	Antimeningococcic serum (4 doses), spinal drainage, sulfanilamide.	Recovered.	
4	F.	43	Right otitis.	Spinal drainage, sulfanilamide.	Recovered.	
5	F.	3½	Left otitis.	Spinal drainage, sulfanilamide.	Recovered.	
6	F.	11	Right otitis with mastoiditis.	Spinal drainage, sulfanilamide.	Recovered.	
7	F.	2	Double otitis with right mastoiditis, following scarlet fever.	Right mastoidectomy with ligation right jugular, spinal drainage, sulfanilamide, convalescent scarlet fever serum.	Died.	Refused operation and mastoiditis persisted after recovery from meningitis.
8	M.	5½	Left otitis with mastoiditis, following pneumonia.	Mastoidectomy, antimeningococcic serum, spinal drainage, sulfanilamide.	Recovered.	Meningitis appeared 7 days after operation. Necropsy showed herniation of cerebellum and thrombosis of left lateral and transverse sinuses and of left jugular.
9	M.	8	Right otitis with mastoiditis.	Mastoidectomy 1 month prior to meningitis, spinal drainage, sulfanilamide.	Recovered.	Mastoidectomy done about 1 month before onset of meningitis. Spinal fluid showed positive culture for 14 successive days.
10	F.	4	Left otitis with mastoiditis and later right otitis.	Left mastoidectomy, spinal drainage, sulfanilamide.	Recovered.	At operation, left mastoid found necrotic although no clinical signs.
11	M.	35	Pan-sinusitis.	Antimeningococcic serum, spinal drainage, sulfanilamide.	Died.	Sulfanilamide was used for less than 24 hours. Necropsy showed pan-sinusitis and sarcoma of pituitary.
12	F.	12	Left otitis with mastoiditis.	Mastoidectomy, spinal drainage, sulfanilamide, 1 dose antimeningococcic serum.	Recovered.	At operation, mastoid found necrotic although no clinical signs.

14	F.	10 mos.	Double otitis with double mastoiditis	Mastoidectomy, spinal drainage, sulfanilamide.	Died.	There was also clinical evidence of brain abscess. At operation, dural plate found nearly destroyed. Sulfanilamide used for less than 12 hours.
14	F.	8	Left otitis with mastoiditis	Mastoidectomy, spinal drainage, convalescent scarlet fever serum, sulfanilamide.	Recovered.	At operation, mastoid found necrotic although no clinical signs.
15	F.	6½	Right otitis with mastoiditis.	Mastoidectomy, spinal drainage, sulfanilamide.	Died.	Necropsy showed meningitis but no localized suppuration.
16	M.	4	Following measles, first left otitis with mastoiditis and later right otitis with mastoiditis.	First left mastoidectomy and later right mastoidectomy, spinal drainage, sulfanilamide.	Recovered.	Meningitis appeared 12 days after left mastoidectomy. At this time a right mastoidectomy done.
17	M.	7	Double otitis with double mastoiditis following scarlet fever.	First left mastoidectomy and 3 weeks later, right mastoidectomy, spinal drainage, sulfanilamide.	Recovered.	Onset of meningitis was about 12 days after the second mastoidectomy.
18	F.	11 mos.	Upper respiratory infection.	One spinal drainage, antimeningococcal serum, sulfanilamide.	Died.	Death in less than 12 hours after receiving sulfanilamide.
19	F.	6	Double otitis, double mastoiditis.	Double mastoidectomy, spinal drainage, sulfanilamide.	Recovered.	

twenty-four hours in a third instance. In a fourth fatal case, the necropsy showed herniation of the cerebellum through the mastoid wound and thrombosis of the left lateral and transverse sinuses and of the left jugular vein.

These results seem to us who have been working so long and so unsuccessfully with this form of meningitis, little less than astounding. The question is sometimes raised as to the possibility that the hemolytic streptococcus may recently have become more benign. Such a radical and sudden change seems to us most improbable. During the year 1936, we saw 20 cases of this type, all of which died with the exception of the one following scarlet fever to which we have already referred.

In dealing with all forms of bacterial meningitis, it is important to identify the causative organism exactly. It has been our experience that far too little attention is paid to this in many laboratories. In several instances cases have been reported to us as due to a nonhemolytic streptococcus, but when the organisms were grown on proper culture media they proved to be of the hemolytic type. Certain strains will hemolyze only horse blood, and the media must not contain glucose.

It is important in all forms of meningitis to drain adequately the subarachnoid space. In our experience the more radical methods of establishing drainage, such as laminectomy or trephining the cisterna magna, have no advantage over repeated lumbar punctures or cisternal or ventricular punctures if block occurs. Indeed, establishing permanent drainage may be a disadvantage if serum or chemicals are to be used intraspinally. Forced spinal or perivascular drainage has been used rather extensively during the past four or five years. We have had considerable experience with this method of treatment. As a result of our experience we do not recommend it.

Whenever the meningitis is secondary to a focus of infection it is important to eradicate this focus as completely and as promptly as possible. It cannot be too strongly emphasized that not infrequently a severe mastoiditis may fail to present clinical symptoms and occasionally even roentgenographic evidence of involvement. This is shown in the Tabulation. Of course, a patient will occasionally recover even if the focus infection is not removed. But as a rule it is too great a risk not to eradicate the primary focus.

There can be little question that the development of sulfanilamide is one of the major achievements of modern therapeutics. It cannot be too strongly emphasized that in prescribing sulfanilamide, reliable products must be selected. The recent tragedy following the use of sulfanilamide prepared in a toxic solvent is too well known to require further comment.

Summary.—The value of sulfanilamide in virus infections is highly problematical. We have discussed briefly the dosage and mode of administration of this chemical in various bacterial infections of the central nervous system. Sulfanilamide is of doubtful value in meningitis due to the staphylococcus, *Bacillus influenzae* and the nonhemolytic streptococcus. In pneumococcic meningitis this chemical is effective at times. In infections with the meningococcus we believe that sulfanilamide is of value in spite of our own statistics. The results in hemolytic streptococcic meningitis have been exceedingly gratifying. It is of the greatest importance to remove primary foci of infection.

We wish to thank the Winthrop Chemical Company for generously supplying us with prontosil, prontylin and prontylin crystals.

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CLINIC OF DR. EDWARD A. HOROWITZ

BETH ISRAEL HOSPITAL

HYPERPYREXIA OR SULFANILAMIDE IN THE TREATMENT OF GONORRHEA IN WOMEN

SEVEN years ago at the Beth Israel Hospital in New York, a woman with pelvic inflammation was referred from the gynecological service to the physical therapy department for treatment by means of electrically induced fever. The treatment was administered by the attending physical therapist, Dr. William Bierman. I was present as the representative of the gynecological service, to observe the effect of the treatment. The patient tolerated the treatment very well and her pelvic inflammation resolved with unusual rapidity. As other patients with pelvic infections (mostly gonorrheal) were treated in increasing number, I had the opportunity not only of conducting follow-up examinations on most of the treated patients, but also of collaborating with Dr. Bierman in perfecting the technic of the treatment.

The technic of fever treatment is important because upon it depends therapeutic effectiveness, as well as the safety of the patient. The highest systemic temperature which may be maintained with relative safety in human beings is 106.7° F. The special technic which Dr. Bierman and I have developed for the treatment of gonorrhea in women, combines physically induced systemic fever with simultaneous additional heating of the infected pelvic organs by means of high frequency currents. This additional heating of the tissues in which the gonococci are lodged (to 109° or 110° F.) results in a more rapid destruction of the gonococci.

The greater effectiveness of the combined pelvic and systemic heating procedure as compared with treatment by systemic fever alone, has been corroborated by other workers.

For example, Dr. Frank Krusen and associates of the Mayo Clinic reported at the First International Conference on Fever Therapy, at New York City, March 31, 1937, on their experiences with our combined technic.¹ A number of female patients in whose secretions gonococci had persisted in spite of repeated treatments by systemic fever alone, promptly became negative after administration of the combined treatment. Pelvic inflammatory masses which had been resistant to systemic fever treatment, resolved after treatment by hyperpyrexia combined with pelvic diathermy. We are certain that the number of fever treatments necessary to free our female patients of gonococci has been lessened by the simultaneous pelvic heating. Of 67 women whom Dr. Bierman and I treated for gonorrhea by means of six-hour sessions of hyperpyrexia combined for four hours with pelvic diathermy, 62 were freed of gonococci after an average of 2.4 treatments per patient.² Other workers who administered six-hour treatments by hyperpyrexia alone, found it necessary to treat their patients an average of five or six times.^{3, 4}

Because of the additional pelvic heating, it is feasible to maintain the patient's systemic temperature at 105.5° or 106° F., instead of at 106.7° F. as required for treatments by systemic fever alone. The employment of fever temperatures 1° F. lower than generally considered necessary for the treatment of gonococcal infection, definitely adds to the safety of the patient.

For safe and effective pelvic heating, I have devised special vaginal electrodes molded from plaster casts of the vagina of living women.⁵ These electrodes are available in four lengths, varying from 2¼ to 4¼ inches. For each patient an electrode of proper length should be chosen. The electrodes are of relatively large surface area and have no sharp edges, which if present might cause a local overheating of tissue. Each electrode has an insulated handle which is hollowed for the insertion of a thermometer, the bulb of which penetrates into a cavity bored in the active metal portion of the electrode. The scale of the thermometer projecting from the vaginal electrode is observed every five minutes during treatment. The vaginal temperature is not permitted to exceed 110° F., which is well tolerated by the vaginal mucous membrane.

For the pelvic heating I have used various types of short and ultra-short wave apparatus" as well as conventional diathermy. With conventional diathermy, a special arrangement of four dispersive electrodes is employed to prevent overheating of the subcutaneous tissue under the indifferent diathermy electrodes.² The four dispersive electrodes are connected to one terminal of the diathermy apparatus and the vaginal electrode to the other terminal.

The systemic temperature is most conveniently elevated by the application of ultra-short wave while the patient lies in a cabinet heated by electric lamps. When the systemic temperature has reached 105.5° F., the pelvic heating is started. At the first treatment of a woman with gonorrhea who is otherwise in good physical condition, the systemic temperature is maintained at 106° F. for twelve hours, during five and one-half hours of which the vaginal temperature is elevated between 109° and 110° F. In 73 cases in which this technic was employed, about two thirds were freed of gonococci after a single session. The average number of treatments in this group was 1.4 per patient.

Of 150 women with gonorrhea, whose subsequent course I have been able to follow, 92 per cent were freed of gonococci following the fever treatments. The period of observation of these cases was sufficiently long (from three months to six years) to make it likely that the disappearance of the gonococci has been permanent. In addition to frequent smears, especially postmenstrual, I have made extensive use in the follow-up of these patients during the past three and one-half years, of cultural examinations for gonococci.

The treatment is uncomfortable but there is no pain. Sedatives may be administered at intervals for restlessness. In addition to an experienced nurse technician, the patient should be watched at all times by a physician who has been trained in the work.

This treatment is indicated at any stage of gonorrheal infection in the otherwise healthy woman. About five years ago a patient was treated during menstruation and developed evidences of salpingitis the following day. Since then I have avoided the treatment of any patient during or just before menstruation. Other than the case just referred to, there has

been no instance of extension of the infection in any patient who has received fever therapy.

In women with acute or subacute gonorrheal salpingitis or arthritis, pain usually disappears during the first treatment. Within a few days after adequate treatment, abnormal discharges have usually disappeared. Adnexal masses become painless and nontender, but usually do not disappear until five to ten days after treatment. Nine normal pregnancies and one ectopic have occurred among the 60-odd salpingitis cases in this series from five months to five years after treatment. Third degree skin burns, none serious, occurred in 3 cases, and jaundice in 1 case. There was no fatality.

The fever therapy of gonorrhea in women by means of the technic which I have described, is a highly effective, although somewhat strenuous procedure, which should be administered only in hospitals under the care of experienced nursing and medical personnel.

In May, 1937, Dees and Colston,⁷ and also Reuter,⁸ reported on the successful treatment of patients with gonorrhea by means of sulfanilamide given by mouth. The possibility of eradicating gonorrhea by this cheap and simple method excited great interest and led to widespread and often uncontrolled use of the drug.

Not all of the reports on the sulfanilamide treatment of gonorrhea have been enthusiastic. In October, 1937, at a symposium at the New York Academy of Medicine, one urologist reported 90 per cent of cures following the treatment, another 72 per cent, a third 29 per cent, and a fourth no cures at all. Conflicting judgments as to the value of the sulfanilamide treatment are likewise to be found in the rapidly growing literature. These differences of opinion may be caused by:

1. Differences in the details of the sulfanilamide treatment—in daily dosage, distribution of doses, duration of administration.
2. Differences in the type of patient, type of infection, control of patients' activities, fluid intake, etc.
3. Differences in the duration of follow-up, and in the criteria of cure employed.

It is true that some have prescribed smaller doses of sulfanilamide than those recommended by Colston, in order to

lessen the incidence of toxic reactions. However, even those who have employed sulfanilamide in identical dosage have not been equally successful in "curing" their patients of gonorrhea. It seems to me that differences in the duration of follow-up and in the criteria of cure have an important bearing upon the reported results.

The finding of gram-negative biscuit-shaped intracellular diplococci in smears has usually been relied upon for the diagnosis of gonorrhea. However, smears are often reported negative in patients with chronic gonorrhea, especially in women, in whose secretions gonococci may be demonstrated by cultural methods. Repeated culture examinations for gonococci should therefore supplement smear examinations in the follow-up of patients who have been treated for gonorrhea. This is especially desirable when attempting to evaluate a new therapeutic method.

It was recently pointed out by Jones,⁹ that following sulfanilamide treatment of gonorrhea, smears may become atypical in appearance. According to the usual criteria, such smears are reported negative although gonococci persist in atypical form or distribution. However, the patient is still infectious and culture examinations are positive. It is therefore unfortunate that in some of the published reports on the sulfanilamide treatment of gonorrhea, the disappearance of symptoms and three negative smears have been considered proof of cure.

Between May and October of 1937 I administered sulfanilamide treatment to 12 women with gonorrhea whose subsequent course I was able to follow closely for periods varying from four to ten months. I venture to report so small a group of cases only because these patients have had a searching follow-up including repeated cultures, in addition to gynecological and smear examinations.

Six of the 12 patients received a daily dose of 60 grains of sulfanilamide for periods varying from three to five weeks. In the 6 other cases, the schedule of dosage recommended by Colston¹⁰ was carried out. Colston recommends giving the drug in four doses each day and continuing it for four weeks. During the first two days he advises giving 80 grains a day, then 60 grains a day for five days, 40 grains a day for a week,

and finally 20 grains a day for two weeks. This scheme of dosage is, of course, purely empirical. In the treatment of patients with streptococcal general infections, it is advised by Perrin Long¹¹ that a concentration of 10 to 15 mg. of sulfanilamide in each 100 cc. of the patient's blood be maintained for optimal therapeutic effect. Periodic determinations of the blood sulfanilamide are made by means of Marshall's^{12, 13, 14} test, and the dosage regulated so as to maintain the desired concentration in the blood. For the successful treatment of gonococcal infections, however, the optimal blood concentration of sulfanilamide has not yet been determined.

Fluids were not forced because this might have hastened the elimination of the drug from the body.

Repeated determinations were made of the blood sulfanilamide of each patient while she was receiving the medication. To facilitate the determinations, I have adapted Dr. Marshall's second method^{13, 14} to the determination of free sulfanilamide in 0.1 cc. of blood, which may easily be obtained from the fingertip. Since the quantity of blood used is one twentieth that required in the method as described by Dr. Marshall, the quantity of each of the other reagents is reduced in proportion. The blood is conveniently taken from the finger into a Byrd diluting chamber,¹⁵ previously used for obtaining samples for micro Folin-Wu determinations. One-tenth cc. of blood is drawn to the mark, then at once diluted with saponin solution drawn to the second mark (total volume 0.8 cc.). After mixing, the diluted and laked blood is drained into a test tube and 0.2 cc. of toluenesulfonic acid solution added, with shaking. After five minutes the test tube is centrifuged. Most of the clear supernatant fluid is drawn into a Wright's pipet, and 0.4 cc. of it is transferred to a special comparison tube. This tube is the same in length but exactly half the volume of an ordinary Sahli hemoglobinometer tube, and graduated in the same way to 140. The 0.4 cc. of supernatant fluid reaches the 40 mark. The sodium nitrite is added, 0.04 cc., the mixture shaken, and allowed to stand three minutes for the diazotization to be complete. Dimethyl- α naphthylamine solution, 0.2 cc., is added, and the fluids mixed. The standard is prepared with 0.4 cc. of a solution of sulfanilamide containing toluenesulfonic acid, treated like the blood filtrate. The colors are

compared by placing the tubes in an ordinary Sahli colorimeter, the solution of stronger color being diluted to match the weaker.

The microsulfanilamide determination is not expected to be so accurate as the usual procedure using 2 cc. of venous blood. However, it enables us to make blood sulfanilamide determinations with a frequency to which our patients might object, if venipuncture were required each time. The micro-method has also been valuable in determining the blood sulfanilamide in cases of meningitis or puerperal sepsis, whose veins might need to be spared for blood transfusion, in women with difficult veins, and in children.

Results with Sulfanilamide.—In our patients with gonorrhea, the blood sulfanilamide varied between $4\frac{1}{2}$ and 11 mg. per 100 cc., most of the values lying between 6 and 8 mg. per 100 cc.

One patient with chronic gonorrhea vomited a great deal following institution of sulfanilamide treatment, became mentally confused, and appeared very much prostrated. Her blood sulfanilamide reached 11 mg. per 100 cc. It seemed advisable to stop the drug on the fifth day. Gonococci persisted. A patient with subacute cervicitis, urethritis and proctitis received 60 grains each day for four weeks, her blood sulfanilamide values varying between $6\frac{1}{2}$ and 9 mg. She felt well throughout, but gonococci persisted. Two patients with acute salpingitis and one with acute peri-arthritis of the hand, each associated with cervical and urethral infection, had several negative smears and cultures after receiving sulfanilamide two and one-half and three weeks respectively. The salpingitis and peri-arthritis subsided and the patients appeared well. However, within two weeks after the medication was stopped each patient again had positive gonococcal cultures, although the smears remained negative in 1 case and doubtful in the other. Without check-up by culture these cases might have been considered cured. A patient treated in the second and third months of pregnancy for gonococcal cervicitis and urethritis became negative bacteriologically with a complete cessation of discharge. Seven smears and five cultures were negative. Then in the seventh month of pregnancy there was a recurrence.

Of the remaining 7 patients 3 entered the hospital with acute salpingitis and 1 with gonococcal arthritis while 3 were ambulatory cases with only lower-genital tract infections. All of these had persistently negative smears and cultures following treatment, the shortest follow-up period being four months. We seem, therefore, to have a bacteriologic cure in 7 of 12 cases, or 58 per cent.

Toxic Effects.—In addition to the patient with mental confusion and vomiting already referred to, other toxic effects of sulfanilamide were noted in these patients. Most of them became more or less deeply cyanotic. Spectroscopic examination of the blood of the cyanotic cases revealed the presence of methemoglobin in three. Sulfhemoglobinemia was not found in any case. One ambulatory patient developed fever reaching $103\frac{1}{2}^{\circ}$ F., which subsided to normal within a day and a half following discontinuance of the medication and the forcing of fluids. Another ambulatory patient developed a severe skin reaction characterized by a dermatological consultant as being of the erythema multiforme type. This was most marked on the face, nearly closing her eyes, and involved also the arms and legs. It had disappeared in six days after sulfanilamide was stopped. In 1 hospital case of salpingitis we noted a drop of hemoglobin from 80 to 65 per cent, with a corresponding drop in the red blood cells, and discontinued the medication.

As recommended by Dr. Long we have given 10 grains of sodium bicarbonate with each dose of sulfanilamide to prevent development of acidosis from the drug. Hemoglobin determinations and white cell counts have been done two or three times a week to enable us to detect hemolytic anemia or granulocytopenia, should they develop.

My 2 patients with the highest blood sulfanilamide values (9 and 11 mg. per 100 cc.) were not freed of gonococci. Obviously the blood sulfanilamide level is not the only factor which determines success or failure in the treatment of gonorrhea.

At the May, 1938, meeting of the American Neisserian Medical Society, an attempt was made to evaluate the sulfanilamide treatment. With doses similar to those received by my patients, the proportion of cures of gonorrhea reported from various clinics was approximately the same. For exam-

ple, Dr. Perrin Long reported from the Johns Hopkins Hospital that of the cases followed after sulfanilamide treatment by repeated smear and culture examinations, 65 per cent had remained free of gonococci.

Not satisfied with the results of ambulatory treatment and the doses of sulfanilamide usually employed for the treatment of gonorrhea, Drs. Van Slyke, Thayer and Mahoney¹⁶ of the U. S. Public Health Service have for some time been hospitalizing patients with gonorrhea for intensive sulfanilamide therapy. Patients of average weight are given 20 grains of sulfanilamide every four hours, day and night, for the first four to six days. Small patients receive 15 grains every four hours. Fluids are limited to 1500 cc. or less. Sulfanilamide is never continued beyond the twelfth day. Patients tolerate the large doses better if kept in bed. A high percentage of cures has followed this intensive hospital treatment of gonorrhea. Dr. Perrin Long reported at the May, 1938, Neisserian Society meeting that at the Johns Hopkins Hospital patients with gonorrhea were being admitted to the Urological Service for bed treatment with large doses of sulfanilamide. Starting with 150 grains a day or more, sulfanilamide is given every four hours day and night just as in the treatment of patients with severe streptococcal infections.

It was suggested by Ballenger¹⁷ and others that patients resistant to fever therapy or to sulfanilamide alone be treated by the simultaneous use of the two methods. Ballenger gave 80 grains of sulfanilamide a day for two days, followed by a session of three or four hours of systemic fever at 103° or 104° F. The dose of sulfanilamide was then reduced to 60 grains a day and 2 similar additional fever sessions were given. Excellent results were reported in a small series of cases. The evaluation of this report is difficult because the authors do not mention the duration of their follow-up or the number of negative smears and cultures required as a criterion of cure. There is no mention of the likelihood of increased danger to the patient by the possible summation of harmful effects produced by sulfanilamide and by hyperpyrexia. There is no mention of examinations for methemoglobinemia, or of determinations of the oxygen content, oxygen capacity or oxygen saturation of the patient's arterial blood.

Peters and Van Slyke¹⁸ quote Meakim's statement that "the occurrence of oxygen want, particularly in association with fever, is a most dangerous condition in itself. . . ." According to the same authors, Cobert found that the ordinary spectroscopic examination is uncertain when less than 25 per cent of the blood pigment is in the form of methemoglobin. The demonstration of methemoglobinemia is, therefore, evidence of a definite diminution of the oxygen carrying capacity of the patient's blood. In a recent number of the Journal American Medical Association, Mull and Smith¹⁹ reported finding a sharp drop in the oxygen content, oxygen capacity and oxygen saturation of the blood of a patient cyanotic following sulfanilamide administration. The spectroscopic examination of this patient's blood had failed to show methemoglobin or sulfhemoglobin.

Dr. Frank Hartman²⁰ made a careful study of the brain lesions of patients and of experimental animals who had died following hyperpyrexia treatment. He was convinced that these lesions had been produced by anoxia. Factors producing anoxia during fever therapy are alkalosis, accelerated blood flow, increased temperature of the blood, and increased demand for oxygen in the tissues.

Alkalosis during fever therapy results from rapid breathing and blowing off of carbon dioxide. It is important because the slightly alkaline hemoglobin compound gives up its oxygen less readily to the tissues than normal oxyhemoglobin. The increased blood flow during fever has been shown²¹ to be followed by a lessening of the difference in oxygen saturation between the blood of the femoral artery and vein, as a result of which the oxygen unsaturation of the tissues gradually increases. Increased temperature of the blood itself decreases oxygen saturation.²² The same increase in temperature also increases the basal metabolic rate 5.5 per cent for each degree Fahrenheit, giving a rate of plus 29 per cent with a temperature of 104° F.²³ Increased metabolism means a corresponding demand for oxygen in the tissues.

In animal experiments, Hartman found that fever therapy causes a constant and severe anoxia as shown by the decreased oxygen saturation of the arterial blood and low oxygen content of the venous blood.

Before reading Hartman's paper I had treated 3 patients with sulfanilamide followed by fever therapy and had been impressed by the marked cyanosis of these patients, and the more rapid pulse rate as compared with that observed in the same patients during previous or subsequent treatments without sulfanilamide.

Elkins and Krusen of the Mayo Clinic²⁴ treated 10 patients with gonorrhea by the simultaneous administration of sulfanilamide and fever therapy. All of these patients had previously received sulfanilamide alone without success. One of the 10 patients had a convulsion while in the fever cabinet. Another had so rapid a pulse that the fever sessions had to be terminated at the end of five hours. The number of hours of fever required to free the 10 patients of gonococci was no less than in cases previously treated by fever without sulfanilamide. Elkins and Krusen quote H. W. Kendell, who has also tried the combined sulfanilamide and fever treatment. It appeared to Kendell that the combination was little more effective in the treatment of gonorrhea than fever alone.

It is possible that sulfanilamide contributed to the cerebral anoxia which caused the convulsion of the patient treated by Elkins and Krusen. The very rapid pulse of one of their patients and the increase in pulse rate of each of my 3 cases treated by the combination of sulfanilamide and fever may likewise be attributed to the drug. I believe that if we add to the anoxia of fever therapy the additional danger of anoxia caused by sulfanilamide, we are exposing our patient to a double hazard. If the patient is also anemic or if she has been made anemic by the sulfanilamide, so much the worse. That is why I have entitled this paper *Hyperpyrexia or Sulfanilamide* instead of *Hyperpyrexia and Sulfanilamide* in the Treatment of Gonorrhea in Women.

Summary.—During the past seven years a very satisfactory technic for the fever treatment of gonorrhea in women has been developed at the Beth Israel Hospital. Prolonged pelvic heating by high frequency currents is combined with systemic hyperpyrexia induced by physical methods. The rationale of the treatment, indications, various technical details and the therapeutic results have been discussed. Of 150 followed-up cases more than 90 per cent were freed of gono-

cocci. With the technic employed in the last 73 cases, 2 out of 3 patients require only a single treatment. The treatment is uncomfortable, but painless. It is relatively safe if constant watchfulness is employed.

Only twelve women with gonorrhea were treated with sulfanilamide, but these were carefully controlled and followed. Blood sulfanilamide determinations were made with the hope of correlating the findings with clinical results. No such correlation was demonstrated. A microtechnic for the determination of free sulfanilamide in the blood, using Marshall's second method, is described. A bacteriologic cure was achieved with sulfanilamide in 7 of the 12 cases, or 58 per cent. Toxic effects included cyanosis (with methemoglobinemia in 3 cases) and the following in 1 case each—mental confusion and vomiting, drug fever, acute hemolytic anemia (mild) and skin eruption. The necessity of prolonged follow-up with repeated culture, as well as smear examination for determination of cure, was emphasized. Newer technics of intensive sulfanilamide treatment were described.

The suggested combination of sulfanilamide with hyperpyrexia is not advocated because of the possible summation in some cases of the harmful effects (in particular, anoxia) produced by the two measures.

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SILICOSIS AND SILICOTUBERCULOSIS

SILICOSIS, one of the pneumoconioses, is a chronic form of pulmonary disease caused by the inhalation of silicious dusts, and is characterized by both anatomical and physiological changes in the lung. The anatomical changes, consisting of fibrosis and nodulation along the bronchial tree in the beginning of the disease, frequently end, as the exposure to dust continues, with extensive areas of fibrosis. The increasing fibrosis, affecting both the pulmonary and cardiac functions, becomes a threat to the working capacity and even the life of the worker.

Silicosis occurs in many occupations, but is most frequently associated with rock-drilling and mining. Physicians must also become familiar with all the occupations which may be responsible for silicosis. Not infrequently men exposed to silicious dusts change their occupations, and migrate to another town or state where they take up new occupations, and silicosis may never be suspected. When one suspects silicosis the following occupations are to be thought of besides rock-mining and drilling: tunnel working and excavating, sand-blasting, stone cutting, pottery and porcelain industries, stone and metal polishing and grinding, soap manufacturing, especially the abrasive soaps and powders, the spraying of paints, which frequently have a high silica content, the use of clays, cement industries, etc.

Etiology.—Up to the recent work of Jones¹ the belief was that silicosis was caused by the inhalation of uncombined silica (SiO_2). The latter investigator found that in the vicinity of Johannesburg where silicosis was very common, the rock was very rich in sericite, whereas in the vicinity of Kolar, where the rock was poor in sericite, the pulmonary complica-

tion of mining was an uncommon happening. Jones associated the presence of sericite with the frequency of the occurrence of silicosis. Whether the disease is caused by sericite or free silica (SiO_2) has not been definitely settled, except that most investigators lean to the belief that uncombined silica is the true cause of silicosis. How this free or uncombined silica stimulates fibrosis has also been a debatable question. The question as to whether the irritation of the lung tissue is caused by the physical properties of the hard, sharp silica particles, or whether the irritation is due more to physiochemical irritation has divided investigators into two groups. Colles,² Haldane,³ and Mavrogordato⁴ are of the opinion that the disease is produced by the chemical irritation of the free silica in the lung tissues rather than by the mechanical irritation of the particles.

The size of the particles plays an important rôle in the production of silicosis. The most harmful effect comes with the fine particles. Lanza⁵ has stressed the importance of the fine state of the particles in causing silicosis. It is known that particles must be less than 10 microns in diameter before they can do damage, and McCrae⁶ has pointed out that the silica dust particles taken up by the reticulo-endothelial cells in the alveoli of the lungs are usually less than 5 microns in diameter. Smyth and Iszard⁷ made similar observations, and found the majority of the particles to be about 1 micron in diameter.

The number of particles found in the dust, as well as the percentage of silica in the dust, has an important bearing on the development of silicosis. In the various industries there must be marked variations in the silica content and the number of particles in the dust which influence both the development and progress of silicosis. Standards set up for one industry, as to time of exposure, number of particles, and silica content of the dust, would not hold good for other industries. However, we must accept some standard, to be able to consider the probability of silicosis. Since silicosis has become a compensable disease in New York state, the physician unfamiliar with silicosis looks with suspicion upon any pulmonary disease where there is a history of any exposure to dust. Recently I received an inquiry as to whether a janitor's child,

an infant less than a year old, exposed to coal dusts during the process of unloading the coal from the trucks to the bins, could have developed silicosis. Russel, Britton, Thompson and Bloomfield^s reported, that when the number of particles did not exceed ten to twenty million per cubic foot of air, the workers in the Barre granite industries escaped silicosis, and when they were exposed to higher concentration of particles, they developed silicosis. We must admit that the concentration of silica particles in the air is a very important factor, and, therefore, more than a history of exposure to silicious dusts is necessary. Four factors are of importance: the concentration of the particles, the size of the particles, the silica content of the dust, and the time of exposure to the dusts. Severe criticism is justifiable against making a formula to fit all industries. An attempt at a formula to fit all industries, based on the work of Russel *et al.*, might be used in considering the possibility of the presence of silicosis. The formula might be as follows: *silicosis could develop only in silicious dusts containing over 20 per cent uncombined silica, with particles under 5 microns in diameter, and exceeding a concentration of 20,000,000 particles per cubic foot of air, and with a continuous exposure of no less than five years. Should the silica content increase, the particles become finer, the concentration of particles greater, the duration of time required for the production of silicosis becomes proportionately shorter.* The above formula would immediately rule out cases based on indefinite exposure to silicious dusts.

The pathology can only be lightly touched upon in a paper of this sort. The smaller-sized particles which have been inhaled and which escape the protective mechanism of the upper respiratory tract, are engulfed by the phagocytes in both the respiratory bronchioles and the alveoli. These particles are carried by the reticulo-endothelial cells into the intrapulmonary lymphoid tissues, from which area the phagocytic cells enter the pulmonary lymphatics and are filtered out along the bronchopulmonary deposits of lymph tissue and the tracheobronchial lymph nodes at the root region. After a time, a good deal of irritating silica particles are deposited in the pulmonary lymphatic system. Due to the irritation of the silica, local proliferation is stimulated. The lymphatic flow is inter-

ferred with, and nodular formation occurs along the bronchopulmonary lymphatic system. Some phagocytes find their way through the vessel walls into the surrounding connective tissue, where further proliferation is stimulated. Gardner⁹ outlines the many stages of the reactions as follows: "Through the migrating phagocytes, silica is concentrated in intrapulmonary and mediastinal lymphoid tissues. Proliferation takes place, which interferes with free circulation of lymph. The lymph nodes enlarge and the lymphatics dilate because of the central obstruction. Dust cells pass through the walls of the distended vessels and a certain amount of perilymphatic inflammation develops. Since the lymphatics course through the walls of the blood vessels and bronchi, these structures appear thickened. The hypertrophied lymph nodules along the course of the vessels give them a beaded appearance. The accumulated dust in the parenchyma of the lung cannot be eliminated and consequently nodules form in the functional parts of the organ."

Symptomatology.—The symptoms in silicosis depend a great deal on the stage of the disease. In the early stages there probably are no definite symptoms except for the appearance of cough. The cough is accounted for by the dusty occupation, and after a time the worker looks upon it as a normal habit. As the disease progresses there is a gradual decrease in vital capacity, but unfortunately the reduction must be tremendous before one becomes conscious of dyspnea. The vital capacity can almost be cut in half before it is realized that shortness of breath occurs on exertion, and one may still walk on level ground without becoming short of breath. Therefore, to say that there is a gradual progressive dyspnea as the silicosis progresses would not be a true picture of the clinical situation. There may be a progressive diminution in vital capacity, but dyspnea as a symptom usually comes very late in the disease. The silicosis is quite advanced before the vital capacity is reduced sufficiently to cause dyspnea on exertion. Therefore, in early and moderately advanced silicosis, there are but few symptoms: cough, expectoration, and occasionally blood-spitting, which the worker associates with the dusts which pollute the air.

The working capacity during these stages is not materially

reduced. From this point on, should the disease progress, dyspnea becomes the important symptom. With few exceptions dyspnea is almost always associated with late and extensive silicosis. In this advanced stage, much confusion occurs. The extensive and irregular pulmonary fibrosis is easily confused with pulmonary tuberculosis. As previously stated, the silicotics first become aware of their illness because of their inability to keep up with their work, and during this period they first become aware of their dyspnea. They find that they fatigue easily. They become more conscious of their cough and expectoration. Hemoptysis is more apt to occur at this stage of the disease. For the first time medical aid is sought. The physician, confronted with symptoms almost identical to the symptoms in advanced pulmonary tuberculosis, and with physical and x-ray findings which could easily fit in with tuberculosis, usually loses sight of the occupational disease, and either makes a diagnosis of pulmonary tuberculosis, or uses the term "silicotuberculosis." Tuberculosis as a complication in silicosis will be discussed later. The symptoms of silicosis are really the symptoms of pulmonary fibrosis, and manifest themselves chiefly when the vital capacity is sufficiently decreased to interfere with the working capacity of the individual. Because this decrease in vital capacity occurs only late in the disease, the patients usually present themselves to the physician for medical guidance late in the fourth decade in life.

x-Ray Diagnosis.—The peculiar fibrosis and nodulation in the early stages of silicosis of the lungs, cast shadows in the roentgenogram that easily identify the disease. However, in the late stages of the disease the differentiation of silicosis from other pulmonary disease is more difficult, and at times one has great difficulty in the differentiation of advanced silicosis from tuberculosis of the lungs.

In discussing the x-ray appearance in silicosis it would be best to present the tabulations of a committee, composed of Dr. H. K. Pancoast, Dr. E. P. Pendergrass, Dr. A. R. Riddell, Dr. A. J. Lanza, Dr. William J. McConnell, Dr. R. R. Sayers, Dr. H. L. Sampson, and Dr. L. U. Gardner.¹⁰ This committee attempts to present the roentgenological appearances in silicosis correlated with the underlying pathological lesions:

HEALTHY LUNGS AND ADNEXA

Röntgenological appearances

1. Healthy lungs. As defined by the N. T. A. Committee report.
2. Irregular exaggeration of the linear markings, with possibly some beading confined to the trunks.
3. Increased root shadow.

Histological appearances

1. Essentially the normal tissues of the vascular tree, the mediastinum, the bronchi, and trachea.
2. Cellular connective tissue proliferation about lymphatic trunks in the walls of vessels and bronchi. Beading may be due to various causes, as blood vessels seen end on, arteriosclerosis, minute areas of fibrosis in lymphoid tissues along the trunks.
3. Cellular reaction in the tracheo-bronchial lymph nodes with extensions along afferent lymphatic trunks.

These changes come within normal variations when not accompanied by recognized organic disease.

SIMPLE SILICOSIS

4. Nodulation.—Discrete shadows not exceeding 6 mm. in diameter, tending to uniformity in size, density, and bilateral distribution, with well-defined borders surrounded by apparently normal lung shadow. The outer and lower lung fields characteristically show fewer nodules.
5. Conglomerate shadows that appear to result from a combination or consolidation of nodulation usually with associated emphysema manifested by
 - (a) Localized increased transparency of the lung with loss of fine detail.
 - (b) Intensification of the trunk shadows by contrast.
 - (c) Depression of the domes with possible tendency toward individualization of the costal components of the diaphragm.
 - (d) Lateral view: Increase in the preaortic and retrocardiac space with exaggerated backward bowing of the spine. Widening of the spaces may or may not be present.
4. Circumscribed nodules of hyaline fibrosis located in the parenchyma of the lung. Occasionally some of these nodules may show microscopic foci of central necrosis.
5. The result of coalescence of discrete nodules; an area in which the nodules are closely packed and most of the intervening lung is replaced by more or less hyaline fibrous tissue. The lung architecture is partially obscured. No demonstrable evidence of infection. Emphysema is a compensatory dilatation of the air spaces with or without thickening of the septa.

SILICOSIS WITH INFECTION

The characteristic appearances described under simple silicosis are modified by infection as follows:

6. Localized discrete densities and/or stringlike shadows accompanying those of simple silicosis described above.
7. Mottling.—Shadows varying in size with ill-defined borders and lacking uniformity in density and distribution, accompanying simple silicosis.
8. Soft Nodulation.—The nodular shadows described under simple silicosis, 4, have now assumed fuzzy borders and/or irregularities in distribution. This change may or may not accompany the simple mottling of 7.
9. Massive shadows of homogeneous density not of pleural origin symmetrically or asymmetrically distributed.
6. Strands of fibrous tissue, often along trunks and septa, with or without areas of calcification; indicative of "healed" infection.
7. (a) Areas of bronchopneumonia with or without caseation, *i. e.*, acute infection.
(b) Lobular areas of proliferative reaction with or without caseation, *i. e.*, chronic infection.
8. Perinodular cellular reaction either exudative or proliferative in character.
9. Extensive areas of fibrosis probably due to organized pneumonia of tuberculous or nontuberculous origin superimposed upon a coexisting silicotic process. Outlines of normal structures may be partially destroyed.

The simple forms of silicosis are not difficult to recognize but the forms described as numbers 5 and 9 are very difficult to differentiate from tuberculosis. In these advanced stages of silicosis with marked fibrosis the diagnosis is usually pulmonary tuberculosis instead of silicosis. This is the advanced form of silicosis which finds admission to the tuberculosis sanatorium as "advanced pulmonary tuberculosis."

It is my opinion that because of this frequent error in diagnosis between silicosis and tuberculosis the belief has arisen that almost all cases of silicosis die of pulmonary tuberculosis. At the Sea View and Metropolitan Hospitals Ornstein and Umar¹¹ collected 96 cases which were referred to the hospitals as cases of advanced pulmonary tuberculosis. In only 10 out of the 96 cases had silicosis been suspected before entering the hospitals. Twenty-eight out of the 96 cases had advanced forms of silicosis, and during their stay no tubercle bacilli were demonstrable in their sputum. Figures 148-151



Fig. 148.



Fig. 149.

Fig. 148.—A white male worked in the coal mines for fifteen years. The x-ray diagnosis was as follows: there is a localized caseous pneumonic tuberculosis in the right infraclavicular region with a secondary diffuse acinous exudative and productive spread throughout both lungs. The sputum throughout the stay in the hospital was negative for tubercle bacilli. A diagnosis of silicosis was made at Sea View Hospital. See specimen of lungs (Fig. 149).

Fig. 149.—Gross specimen of lungs of case in Fig. 148, showing silicosis and no tuberculosis except encapsulated primary healed focus in right upper lobe. The shadows in the lungs were due to pulmonary silico-anthracosis. The patient died of encephalomalacia.



Fig. 150—White male, fifty-three years of age, coal miner using jack hammer many years. Was referred to tuberculosis service as an advanced case of pulmonary tuberculosis. Twelve sputum examinations revealed no tubercle bacilli. At the Metropolitan Hospital diagnosis was third stage of silicosis.

are typical examples of advanced silicosis referred to the hospital as cases of pulmonary tuberculosis.

Differential Diagnosis.—The diagnosis of simple silicosis is not difficult, and is based on the characteristic nodular shadows cast in the x-ray and with a definite history of sufficient exposure to silicious dusts. Where pulmonary tuberculosis exists, even when there is a history of exposure to silicious dusts, difficulties are encountered. There should



Fig. 151 —White male, fifty years of age, a grocery clerk by occupation, diagnosed at first as advanced tuberculosis. Sputum repeatedly negative for tubercle bacilli. The marked fibrosis suggested the possibility of silicosis and a history was obtained of occupation in the use of clay and the polishing of spark plugs. The man left his occupation to become a grocery clerk because of the severe irritation of his lungs because of dust in his occupation.

never be any doubt as to the diagnosis of the tuberculosis. The diagnosis of clinical pulmonary tuberculosis where there is a suspicion of silicosis can only depend on the demonstration of tubercle bacilli in the sputum. It has been said that tubercle bacilli are difficult to demonstrate in silicotuberculosis. Those of us who have had any clinical experience in pulmonary tuberculosis would not be willing to accept such a view. Tubercle bacilli may be difficult to demonstrate but persistence in the

search would ultimately disclose them. Do we not view the continuous absence of tubercle bacilli even in a previously active tuberculosis as evidence of the arrest of the tuberculosis? Yet in the so-called "silico-tuberculosis" clinicians are willing to accept so unorthodox a view as the presence of clinical tuberculosis without tubercle bacilli. Therefore, it is logical to state that no matter how massive the silicosis may be, and no matter how closely the symptoms, physical findings and x-rays may simulate tuberculosis, a diagnosis of clinical pulmonary tuberculosis complicating silicosis should not be made in the absence of tubercle bacilli.

The diagnosis of silicosis in the positive cases of pulmonary tuberculosis may be very difficult. No matter how much attention may be given to careful x-ray technic, the bronchogenic spread of tuberculosis can simulate the nodulation of silicosis. As has been previously mentioned the clear, simple cases of silicosis cause no confusion. When we suspect a minimal silicosis complicated by tuberculosis the diagnosis of silicosis is fraught with danger. This is especially true if the tuberculous disease progresses rapidly.

The following case report is an example of the above. A patient at Sea View Hospital told of a continuous contact over a large number of years with silica in ship's paint. His occupation required the use of an automatic chipping machine for the removal of paint from the bodies of ships. He was a white male, fifty-eight years of age. Because of symptoms referable to his lungs he went to a physician who discovered an advanced tuberculosis and referred him to Sea View Hospital. The x-ray of the lungs suggested the possibility of silicosis, and in view of the industrial history a diagnosis of silicotuberculosis was made. The diagnosis from the x-ray department was as follows:

"Diffuse acinous and nodular exudative and productive disease, irregularly distributed throughout the upper two thirds of both lungs. The disease has a tendency to become confluent in areas. There is a slight excavation in the left infraclavicular region." The x-ray diagnosis was "pulmonary tuberculosis superimposed on silicosis." Were it not for an autopsy there would have been another case on record of silicotuberculosis. The disease was a progressive tuberculosis which produced a

fatal ending in two months. At autopsy there was no evidence of silicosis.

In the presence of extensive pulmonary tuberculosis, even with a history of exposure to silicious dusts, the diagnosis of silicosis is difficult. Sayers, Meriwether, Lanza and Adams¹² report that out of 7722 miners in the Picher mining district of Oklahoma and Kansas, 5704 were essentially negative and had no silicosis. If any of the above men migrated to another area and took up a different occupation and later developed tuberculosis there would be the temptation of adding silicosis to the diagnosis of pulmonary tuberculosis.

In summarizing, inasmuch as the differentiation always lies between silicosis and pulmonary tuberculosis, in the presence of the former, clinical pulmonary tuberculosis should not be diagnosed without tubercle bacilli in the sputum. In the presence of clinical pulmonary tuberculosis the diagnosis of silicosis is more difficult and must depend first on a sufficient history of exposure to silicious dusts, and second on characteristic roentgenological appearances of silicosis. A positive diagnosis can only be made at the postmortem table.

Tuberculosis and Silicosis.—When one reads the literature written on silicosis and tuberculosis one is left with the thought that tuberculosis is usually responsible for the fatal ending in silicosis. Only as recent as 1933 at a symposium on silicosis at the twenty-ninth annual meeting of the National Tuberculosis Association at Toronto, Canada, tuberculosis was stressed as the common and serious complication of silicosis. Dr. Lanza¹³ stated "It was well recognized that silicosis results fatally due to extraordinary susceptibility to tuberculosis which it induces." A. R. Riddell¹⁴ at the same meeting stated: "Tuberculosis is the commonest and most important complication in silicosis and is responsible for the majority of the deaths among silicotics." Leroy U. Gardner¹⁵ at the same meeting went so far as to give actual figures as to the death rate of tuberculosis in silicosis. Gardner stated: "At least 75 per cent of its victims die of a complicating tuberculosis." The above investigators, however, did not present the material on which the above conclusions were determined. Ornstein and Ulmar¹¹ in a recent paper on silicosis and tuberculosis have pointed out that the very high frequency of tuberculosis

as a sequel to silicosis is a debatable question. They pointed out that the actual incidence of tuberculosis in those exposed to silicious dusts varied from 2 to 5 per cent, and that it was only slightly higher than the incidence of tuberculosis in food-handlers and construction workers. They ask the question that, presuming that almost all silicotics die of tuberculosis, that the average age of silicotics is past forty years, with an incidence of 2 to 5 per cent tuberculosis, when do these men develop and die of tuberculous infection. They also pointed out the peculiarity of the concept concerning the frequent absence of tubercle bacilli in silicotuberculosis, and the frequent use of this unorthodox view of clinical tuberculosis without tubercle bacilli to explain the low degree of infectiousness shown by the silicotuberculous patients. They stress the fact that most of the confusion occurs in the error in differentiation of advanced silicosis with advanced tuberculosis. When clinicians are willing to accept the existence of clinical pulmonary tuberculosis without tubercle bacilli in the sputum as a cause of death, every patient with advanced silicosis dying of pulmonary or cardiac dysfunction would be labelled "advanced pulmonary tuberculosis."

A death should not be ascribed to tuberculosis unless bacilli are demonstrable in the sputum or, in the absence of tubercle bacilli, unless confirmed at autopsy. When there is a question as to the etiology of the fibrosis of the lung at autopsy, it is more plausible to assume that the fibrosis is caused by silicosis than tuberculosis. There should be no question after autopsy whether the death was due to tuberculosis, and yet in the literature one is amazed at protocols in which pathologists are willing to make a diagnosis of tuberculosis without even typical tuberculous structure of the tissues.

Ornstein and Ulmar's¹¹ paper on silicosis and tuberculosis stimulated a good deal of provocative discussion. Fault was found with the fact that they reported the figures of Hoffman¹⁹ as 1095.5 deaths per 100,000 cases of silicosis. By an oversight this figure was used to represent cases of silicosis, instead of 1095.5 deaths per 100,000 granite workers. In a similar manner reference to deaths among Quincy and Milford Union Cutters Union (Pope-Zacks report²⁰) were quoted as deaths among silicotics. The fact that these workers them-

selves compare these groups with the normal population would indicate their belief that they represent a silicotic group.

Instead of presupposing the incidence of tuberculosis from calculated figures taken from a small number of deaths in a small group of workers (Hoffman's figures of 1095.5 per 100,000 granite workers, Pope and Zacks 1152 per 100,000 cutters of the Quincy and Milford Union) why not use actual figures found by investigators among the silicotics? A very important report because of the large number of cases of silicosis examined is the report of Sayers, Meriwether, Lanza and Adams.¹² In the Picher section of Oklahoma and Kansas, out of 7722 men employed in and about the lead and zinc mines during the year beginning July 1, 1927, and ending June 30, 1928, they report an incidence of 3.4 per cent tuberculosis. A group of 1647 (21.3 per cent) were diagnosed as having silicosis. One thousand two hundred and sixty two were in the first stage, 253 were in the second stage, 32 were in the third stage. Besides these 1647 cases of silicosis, 267 additional cases had both silicosis and tuberculosis. The incidence of tuberculosis in this group of 1914 cases of silicosis is 14 per cent. At first glance the figure appears high. Unfortunately no note was made in the report as to whether the cases diagnosed were actual cases of pulmonary tuberculosis with positive sputum or whether the diagnosis was made by x-ray examination. Under the caption "Silicosis Complicated with Tuberculosis" there were two small paragraphs as follows:

"The ordinary silicotic findings described under the different stages of silicosis were noted in the Picher cases. In many of them detection of the beginning of tuberculous infection was difficult because of the extensive changes. The hilum shadows were more likely to show calcified spots than in uncomplicated silicosis. In some of the cases the calcified spots or glands were very large and occasionally occurred in large numbers.

"With the beginning of tuberculosis, areas of marked density were observed, usually at one or both apices. These areas were not so dense or opaque as the fibrotic areas of silicosis and appeared cottony or woolly. They were usually unilateral in the beginning, but often became bilateral before death. In

some instances these areas occurred in the midsection of the lungs opposite the hilum. Large areas of marked density may occur in this region, and it was difficult to determine by x-ray whether the area was a walled-off tuberculous abscess or a dense fibrotic area of silicosis."

The sputum of every case of silicosis and tuberculosis was apparently examined; however, throughout the report there are no figures stating how many cases diagnosed as tuberculous had positive sputum.

Now let us compare these findings with the findings of Martin, Pessar and Goldberg¹⁶ who examined a group of food-handlers. In the first 1000 cases examined, consisting chiefly of men, they found 36 active cases, or 3.6 per cent, and 12 per cent had parenchymal pathology diagnosed as tuberculosis. In the second group of 1000 which consisted chiefly of women there were ten active cases, or 1 per cent, and 11.8 per cent had evidence of pulmonary tuberculosis in the x-ray examination. In this group of 2000 the x-ray evidence of tuberculosis was 11.9 per cent without the worry of confusion with silicosis.

Perhaps the most convincing proof that the majority of silicotics do not die of pulmonary tuberculosis is Boehme's report of the autopsies of 126 stone cutters:

83 had silicosis.

16 (19.3 per cent) of the above also had active tuberculosis.

43 were free of silicosis, and 2 out of this group also had tuberculosis.

The chief trouble lies in the making of the diagnosis of pulmonary tuberculosis. If all reports were based on positive sputum instead of x-ray the deaths and incidence of tuberculosis in silicosis would sharply decline. We have previously mentioned that 96 cases of silicosis were sent to the Sea View and Metropolitan Hospitals 19 of which had previously been diagnosed as silicosis. Seventy-seven of these cases had been sent to the hospital as having far-advanced tuberculosis, without any suspicion of silicosis. Out of 96 cases 28 had no tubercle bacilli in their sputum and were discharged from the institution as far advanced cases of silicosis. Only recently a case of silicosis sent to Sea View Hospital as silicotuberculosis came to postmortem examination. The patient had three admissions to the hospital and finally died there.

Case Report.—Aged fifty-nine years, color white. Third and final admission 7/3/36. First admission 12/7/34. Summary first admission.

Onset October, 1934, when patient caught cold, with cough and pain in the chest. A diagnosis of pulmonary tuberculosis was made by a private physician. Patient went to 116th Street clinic where sputum was found positive for tubercle bacilli. Entered Sea View 12/7/34.

Occupational History:

1. Used dry drill in excavations for two years, 1925 to 1927.
2. Used sledge hammer for breaking rock for ten years previous to above.

Physical Examination:

Lungs—dulness, increased bronchovesicular breathing and occasional fine râles over upper one half of both lung fields.

Retraction of left chest.

Impression—bilateral caseous pneumonic tuberculosis.

1. Bilateral caseous pneumonic tuberculosis.
2. Silicosis.
3. Right inguinal hernia.

x-Ray:

12/10/34—Bilateral caseous pneumonic tuberculosis involving the upper lobes. Deviation of trachea to right. Marked pleural thickening right.

Laboratory:

Sputum persistently negative—6 plain smears, 5 concentrates, 2 gastrics.

Sputum and blood negative.

Progress:

3/5/35—Bilateral productive changes throughout. Exaggerated breath sounds. Emphysema. This is undoubtedly a case of silicosis.

3/20 35—Patient was transferred to Randall's Island for custodial care.

Diagnosis: 1. Silicosis.

2. Chronic pulmonary tuberculosis—inactive.

Second Admission: 9/7/35.

At Randall's Island patient lost 16 pounds in weight. Progressive anorexia and weakness. Readmitted to Sea View.

Physical Examination:

Lungs—Right: Diminished breath sounds with prolonged expiration throughout.

Left: Bronchial breath sounds over upper lung field posteriorly and anteriorly. Occasional moist râles posteriorly. Exaggerated breath sounds at base.

Heart—Negative.

Prostate—Moderately enlarged. Right inguinal hernia.

Impression—1. Bilateral end-stage caseous pneumonic tuberculosis.

2. Silicosis.
3. Pulmonary emphysema.
4. Right indirect inguinal hernia.
5. Chronic hypertrophy prostate.
6. General arteriosclerosis.

Laboratory

Sputum negative for tubercle bacilli.

x-Ray:

- 7/3/35—Bilateral caseous pneumonic lesion throughout both upper lobes with acinous involvement of the lower lobes. Both diaphragms drawn upward. Emphysema of the lower lobes. Marked pleural thickening throughout.
- 9/8/35—Patient was discharged to out-patient department as a nontuberculous case.

Diagnosis: 1. Silicosis.
2. Pulmonary emphysema.
3. Right inguinal hernia.

Final Admission, 7/3/36.

Chief Complaints:

- (1) Pain in chest, (2) cough, (3) loss of weight, (4) anorexia, (5) nocturia. In May, 1936, patient began to complain of pain in chest, cough with scant expectoration. Loss of weight, 30 pounds in ten months. Increasing fatigue and anorexia. No hemoptysis. Nocturia 4-5x.

Past History:

Bronchitis, 1926. Recurring winter cough since.

Occupation:

Laborer. See occupational history above.

Physical Examination:

Lungs—Left: Impaired resonance upper lobe. Bronchovesicular breathing, some bronchial breath sounds, râles and pectoriloquy left upper lobe. Impaired resonance at base.

Right: Impaired resonance upper lobe and over base. Bronchovesicular breathing and râles right upper lobe posteriorly.

Heart—Rate rapid. P_2 accentuated.

Prostate—Enlarged.

Right testicle—Atrophied.

- Impression—1. Chronic pulmonary tuberculosis.
2. Silicosis.
3. Arteriosclerotic heart disease.
4. Chronic prostatic hypertrophy.
5. Atrophy of right testicle.

x-Ray:

- 7/6/36—Extensive bilateral caseous pneumonic tuberculosis more extensive on right side. Marked deviation of trachea to right. Investigate for silicotuberculosis.
- 3/10/37—Progressive clouding throughout both lungs. Findings are very pronounced now in lower lung fields especially on left side.

Laboratory:

Sputum—Gastrics always negative.

Urine—Albumin 1 plus to 3 plus. Few hyaline casts. Few white blood cells, occasional red blood cell.

Congo Red—65 per cent absorption.

Sputum—Negative fungi and cancer cells.

E. K. G.—Myocardial damage on 7/8/36 and 3/15/37.

Course:

- 10/15/36—History and absence of positive sputum suggests that we are dealing with a case of simple silicosis.

3/ 5/37—Progressive weakness. Urinary retention.

3/13/37—Impression: 1. End-stage pneumoconiosis.

2. Advanced arteriosclerosis.

3. Fibrinous pericarditis.

3/28/37—Ankle edema. Change in albumin-globulin ratio to 1:1. Normal blood sugar and nonprotein nitrogen.

3/29/37—Patient expired.

Diagnosis—1. Silicosis.

2. Generalized arteriosclerosis.

Postmortem Record:

The body is that of an adult emaciated white male, of about fifty-nine years of age, presenting clubbing of the fingers and cyanosis of the nails.

The autopsy is limited due to the fact that only an abdominal incision is permitted.

By incising the diaphragm anteriorly, the pleural space is reached. The lungs are found markedly adherent to the chest wall. Only the lungs and heart are removed. The peritoneal cavity is inspected and the abdominal organs are in their usual relationship and no gross evidence of pathological change is noted. Sections of the liver, spleen, and kidney are taken for histological examination.

The left superior tracheobronchial lymph nodes are enlarged to 2 cm. and on section are slaty gray in appearance.

The left inferior tracheobronchial lymph nodes are enlarged to $1\frac{1}{2}$ cm. and are slaty gray in appearance. Present in this node is a stony focus measuring 2 mm. in diameter.

The right superior tracheobronchial lymph nodes are enlarged to 2 cm. and are slaty gray in appearance.

The right inferior tracheobronchial lymph nodes are enlarged to $2\frac{1}{2}$ cm. and are slaty gray in appearance. In one portion is a gray irregular mass measuring 3 mm. in diameter.

The pleurae over both lungs are thickened and the pleural spaces are obliterated.

Left Upper Lobe.—Anteriorly: measures 5 cm. in the apicobasal direction. The lung tissue in this aspect has lost some of its resiliency and is composed for the most part, of slate-gray tissue. Three cm. from the apex and $1\frac{1}{2}$ cm. from the lateral pleura is an irregular excavation, the surface of which is smooth and is lined by a shiny, gray, smooth membrane. Branches of the left upper lobe bronchus communicate with this excavation.

Posteriorly: measures 4 cm. in the apicobasal direction. The lung tissue is firm and indurated and is slaty gray in appearance. The peribronchial lymph nodes are enlarged to $1\frac{1}{2}$ cm. and are slaty gray in appearance.

Left Lower Lobe.—Anteriorly: measures 11 cm. in the apicobasal direction. The lung tissue in the upper third is firm and indurated and is composed of firm and slate-gray tissue. In the lower two thirds, the alveoli are dilated and contain occasional slate-gray, flat-topped foci measuring up to 1 cm.

Posteriorly: measures 14 cm. in the apicobasal direction. The upper third of the lobe is firm, flat and slaty gray in appearance. One and one-half cm. from the interlobar septum and 3 cm. from the lateral pleura is a cavity measuring 8 mm. in the apicobasal direction and 6 mm. in the medial lateral direction. This

cavity is lined by a smooth, gray membrane. One mm. below it is a similar cavity measuring $1\frac{1}{2}$ cm. in the apicobasal direction and $1\frac{1}{2}$ cm. in the medial lateral direction. The alveoli in the lower third are dilated. In the remainder of the lobe are firm, flat, elevated, slate-gray foci varying in size from 2 mm. to 1 cm.

Right Upper Lobe.—Anteriorly: measures 5 cm. in the apicobasal direction. Occupying the greater portion of this lobe is firm, gray, slaty tissue. In the medial aspect of the lobe in the upper half the alveoli are dilated. The bronchi in this aspect are dilated.

Posteriorly: measures 5 cm. in the apicobasal direction. Occupying the greater portion of this lobe is firm, flat, slaty-gray tissue.

Right Middle Lobe.—Anteromedially: measures 5 cm. in the apicobasal direction. Present in this lobe are irregular flat, elevated slate-gray foci varying in size from 1 to 3 cm. The periphery of the strands extend irregularly into the surrounding lung tissue.

Right Lower Lobe.—Anteriorly: measures 2 cm. in the apicobasal direction. Beginning just beneath the interlobar fissure and extending for a distance of 5 cm. is a firm, slate-gray, elevated nodule. This extends irregularly into the surrounding lung tissue. Similar small elevated foci are present in the remainder of the lobe and these measure from 2 mm. to 1 cm. In the lower portion the alveoli are dilated.

Posteriorly: measures 14 cm. in the apicobasal direction. Present throughout this lobe are firm, flat-topped slaty-gray nodules varying in size from 3 mm. to $3\frac{1}{2}$ cm. The periphery of the larger foci radiate irregularly into the surrounding lung tissue. The intervening alveoli in this aspect are dilated.

Diagnosis: 1. Pulmonary silicosis.

2. Silicosis of tracheobronchial lymph nodes.

3. Bronchiectasis right upper lobe.

4. Emphysematous blebs, left upper lobe, left lower lobe.

5. Emphysema, right lower lobe, left lower lobe.

6. Calcification left inferior tracheobronchial lymph node.

If this patient had not come to autopsy, who would have dared to report the case as silicosis without adding tuberculosis? There were no tubercle bacilli in his sputum and the patient had no tuberculosis. The emphysematous blebs in the left upper lobe certainly simulated tuberculous cavities.

As for the atypical tuberculosis found with silicosis our experience at Sea View Hospital demonstrates no difference in the character of the tuberculosis in the lungs than in non-silicotics dying of tuberculosis. Auerbach¹⁸ states that the basic tuberculous changes noted in silicotuberculosis indicate that it is a caseous pneumonic process.

The question of tuberculosis in silicosis is not definitely settled and requires more thorough investigation than in the past. There must be a departure from the method of depend-

ing on the x-ray in the diagnosis of tuberculosis in silicosis, and we must now turn to the laboratory for the demonstration of tubercle bacilli in the sputum and to the postmortem confirmation of the diagnosis of clinical tuberculosis in silicosis when tubercle bacilli are not demonstrable in the sputum.

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CLINIC OF DR. HAROLD LIGGETT

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THE MECHANISM OF HOARSENESS, ITS MEDICAL AND NEUROLOGICAL ASPECTS

HOARSENESS is a symptom for the interpretation of which common sense, academic training and ingenuity must of necessity be combined, to be of aid. The importance of ascertaining the cause of hoarseness will be the difference to the patient of comfort or discomfort, even of life or death. Since the larynx is the organ for the production of voice, it is here that we must look for some evidence to aid us in the diagnosis. We should never assume, however, that local lesions are the only causes of this dysphonia. A great many neurological lesions, both central and peripheral, may be causative agents.

The normal voice is due to a vibration of the vocal cords brought about by a column of expired air from the lungs and its quality is enhanced by the rigidity of the voice box or larynx. The pharynx is the resonating chamber, aided by the nasal cavity and accessory sinuses. When any factor tends to prevent normal vibration of the vocal cords, either in part or in full (as aphonia where the voice becomes a whisper) the patient is said to be hoarse. Common usage compels the use of the term hoarseness to include both dysphonia and aphonia. A laryngectomized patient is aphonic, but he soon learns to whisper quite audibly, when he becomes dysphonic. An hysterical case may be aphonic, or otherwise, depending upon the individual, and the changing mood. A dying, markedly cachectic person, too weak to talk, would be aphonic. The term hoarseness includes all these cases.

The muscles activating the position of the vocal cords are striated and thus under the control of the central nervous system. The muscles of the larynx are:

- (A) Extrinsic muscles:
1. Sternohyoid muscle.
 2. Thyrohyoid muscle.
 3. Stylopharyngeus muscle.
 4. Palatopharyngeus muscle.
 5. Inferior constrictor muscle of the pharynx.
- (B) Intrinsic muscles:
1. Crico-arytenoideus posterior muscle.
 2. Crico-arytenoideus lateralis muscle.
 3. Cricothyroid muscle.
 4. Arytenoideus muscle.
 5. Thyro-arytenoideus externus muscle.
 6. Thyro-arytenoideus internus muscle.

The extrinsic muscles move the larynx as a whole and are said to fix the cartilages to improve the vibratory action of the intrinsic muscles. The intrinsic muscles move the vocal cords and connect the three major cartilages of the larynx, *i. e.*, the thyroid, the cricoid and the two arytenoid cartilages. The last named giving attachment to all but the cricothyroid muscle.

The vagus, or motor nerve, energizes the intrinsic muscles by means of the laryngeal nerve branches. The superior laryngeal nerve carries sensory fibers to supply the laryngeal mucosa with sensation above the level of the cords. The inferior or recurrent laryngeal nerve supplies sensory fibers to the larynx below the cords. All the muscles, with the exception of the cricothyroid muscle, are supplied by motor fibers through the inferior or recurrent laryngeal nerve. The cricothyroid muscle and some portion of the arytenoid muscle are supplied by the external or motor branch of the superior laryngeal nerve.

All of the intrinsic muscles of the larynx are adductors of the vocal cords, with the exception of the posterior crico-arytenoid muscle which is an abductor.

We may assume that the cords adopt three physiological positions, as follows:

1. The position of abduction, known also as the position of respiration and seen easily through the laryngeal mirror in forced or deep inspiration, with the cords widely separated.

2. The position of adduction called the position of phonation and seen in the mirror during the production of sounds as "E, E, E" and "AH, AH" with the cords closely approximated.

3. There is also an intermediate position; of rest or relaxa-

tion, which is placed somewhere between complete abduction and adduction. This is also called the cadaveric position, though in the cadaver the cords are more medial.

In order to maintain or produce these positions certain of the intrinsic muscles are called upon to functionate. We have then, muscles of respiration or abduction, and muscles of phonation or adduction.

The abductor muscle or respiratory muscle is the crico-arytenoid posterior commonly called the "posticus."

The phonatory muscles are divided into four groups, namely:

1. The real antagonists to the abductor which are the adductors of the vocal cords.

- (a) Crico-arytenoideus lateralis muscle.

- (b) Thyro-arytenoideus externus muscle.

2. An adductor of the arytenoid cartilages.

- (a) Arytenoideus muscle.

3. A stretcher of the vocal cords.

- (a) Cricothyroid muscle.

4. A tensor of the vocal cords.

- (a) Thyro-arytenoideus internus muscle.

The arytenoid cartilages are pyramidal bodies which rest upon and articulate with the upper posterior edge of the cricoid or ring cartilage. The joint is diarthrodial and permits only a sliding or pivoting motion of the arytenoids. These pyramids have an apex, which one may see in a laryngeal mirror, a median and two lateral faces. Extending anteriorly from the base are the vocal processes to which the vocal cords or ligaments are attached: the pyramid has a muscular process laterally at the base to which the crico-arytenoid muscles are attached.

When the crico-arytenoideus posticus muscle contracts by its attachment to the muscular process of the arytenoid cartilage, it pivots the arytenoid cartilage so as to evert (abduct) the vocal processes: thus abducting the cords (Fig. 152).

When the lateral crico-arytenoid muscle contracts by the manner of its attachment to the muscular process it adducts and approximates the cords from the anterior commissure of the thyroid angle to the vocal processes of the arytenoid cartilages (Fig. 153).

This action alone is insufficient for normal adduction, for, as may be seen in Fig. 153, there is a triangular chink between the medial faces of the arytenoid cartilages. The arytenoideus muscle closes this gap (Fig. 154).

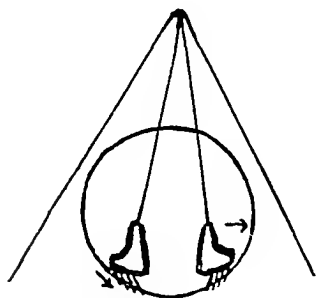


Fig. 152.—Abduction.

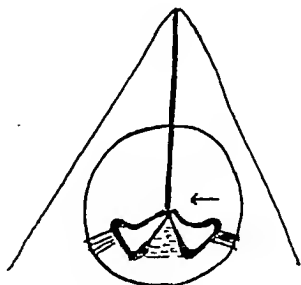
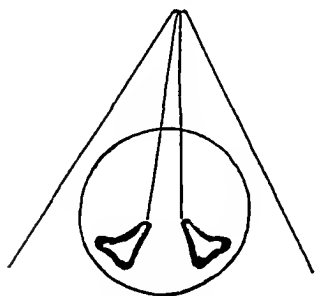
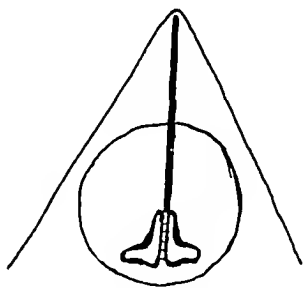


Fig. 153.—Adduction.

The two groups of adductors do not in themselves produce normal phonation. There must also be tension. The vocal cords must be stretched as a violin string to give vibration. Recalling the type of joint which permits only pivoting of the arytenoid cartilage upon the cricoid, the former may be said



Relaxation.



Phonation.

Fig. 154.

to be fixed in the anterior posterior plane so that the arytenoid will move as if fixed to the cricoid in that plane. The contraction of the cricothyroid muscle which draws the anterior part of the ring upward toward the thyroid cartilage causes (by the fulcrum of the cricothyroid articulation), the posterior part of the cricoid cartilage to be forced backward or dorsally.

This carries the arytenoid cartilage back and stretches the vocal cords. By means of this muscle, pitch may be varied, permitting high or low tones at will (Fig. 155).

Still the cords are not yet capable of normal speech: the sound is tremulous. To produce normal speech, tightening of the cords is brought about by means of the tensor muscle, *i. e.*, the "internus" or "vocalis" muscle, terms which are all synonymous with the thyro-arytenoideus internus muscle. The fibers of the tensor muscle, though few in number, send their tendrils into the body of the elastic bands (the cords) where they are incorporated in the structure of the cords. This action is brought about in a manner similar to the contraction of a biceps with a flexed forearm. The "vocalis muscle hardens for high tones."

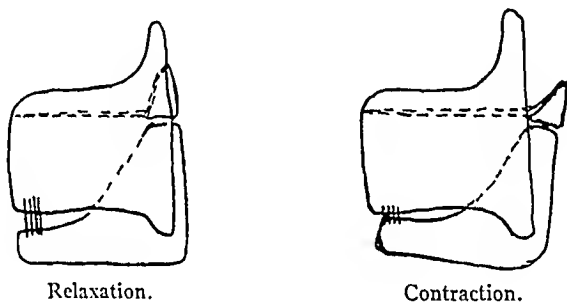


Fig. 155.

Hoarseness, then, is a symptom where there are lesions either peripherally or centrally at or above the nuclei and along the tracts of the laryngeal nerves from their centers in the medulla to the larynx. Lesions in the fourth ventricle will as a rule produce bilateral paralysis of the vocal cords due to the closeness of the nuclei in the brain stem. Supranuclear lesions do not cause paralysis of the larynx because the cortical centers are so wide apart that a lesion must, perforce, be of tremendous size to involve both right and left fibers. Since the cortico-bulbar fibers decussate before reaching the medulla, the larynx can be innervated from either right or left cortex.

Cerebral lesions would all be classified as neurotic causes of hoarseness. To enumerate there are central lesions such as *tuberculous dorsalis* in which an abductor paralysis may be the first

and earliest symptom. Bulbar paralysis is significant in its effect on the vital centers and aphonia would be a warning signal. Hemorrhage occurring in the brain can cause hoarseness as will other conditions affecting the bulb such as softening of the brain. Cerebral lues such as gummata will involve the vocal cords. Lues will cause a variety of lesions: sclerosed blood vessels with consequent hemorrhage and softening will result in laryngeal paralysis. Encephalitis occasionally produces a laryngeal palsy. Syringobulbia and myasthenia gravis are cerebral affections which cause dysphonia.

Lesions along the vagus nerve such as caries or tumors of the base of the skull neighboring the jugular foramen will affect the laryngeal musculature. Posterior jugular adenopathies and suppurative processes in the cervical region cause hoarseness.

Mediastinal tumors such as lymphosarcoma will produce hoarseness. An aortic aneurysm even a small one may cause a left cord paralysis but occasionally a large sac springing from the ascending aorta and the transverse arch will involve the right cord.

The pleural thickenings and adhesions of tuberculosis at the apex of the right lung should be thought of in right laryngeal paralysis. The left cord is occasionally involved in tuberculous fibrositis of the left lung apex. Mitral stenosis with accompanying dilatation of the left auricle causes pressure on the left inferior laryngeal nerve and paralysis. In the neck a large thyroid or enlargement of either lateral lobe of the thyroid gland causes dysphonia. This symptom in thyroid hypertrophy is rare unless the enlargement is a malignant one wherein the glands infiltrate the notch between trachea and esophagus. Esophageal cancer causes laryngeal paralysis.

All the above interfere with the efferent stimulus from the nucleus ambiguus. The left recurrent nerve is more often affected due to its longer course in the neck. In addition there are, as you know, inflammatory, arthritic and rheumatic causes of hoarseness. Local conditions and tumors will interfere with proper phonation. The reason for hoarseness following thyroidectomy is quite apparent. Definite neuritis of the laryngeal nerve has followed influenza or exposure to cold winds resulting in paralysis of any of the groups of intrinsic muscles.

A phenomenon frequently seen in pathology of the nervous system is that when a nerve is injured, all fibers are not of necessity equally affected.

To answer the question why special muscles are first selected in paralysis of the vocal cords, despite the fact that all have identical innervation, Semon and Rosenbach promulgated the theory (Semon-Rosenbach law), that, "In any progressive organic lesion of the centers and trunks of the motor nerves to the larynx, the abductor muscles are first involved." This is certainly clinically evident in the fact that in early aneurysm and cerebral tumors, for example, the vocal cords are unable to abduct properly, whereas phonation shows the cords in the midline. This is actually the first stage of a recurrent paralysis. There is a second stage preceding complete paralysis; the second stage being characterized by involvement of the adductors, the first adductor muscle to be affected is the internus or vocalis muscle, *i. e.*, the thyro-arytenoideus internus. This is observed in the mirror as a bowing of the cords. During phonation the bowing of the vocal cords is a common finding in fatigue of the voice and also in subacute and chronic laryngitis, but it is "internus paresis" not paralysis. In paresis an abduction movement is noticed in respiration. The third and final stage of recurrent paralysis is a paralysis of the lateralis or lateral crico-arytenoid muscle, with the cord or cords, depending on the side involved, now in the cadaveric position in attempted phonation.

Much research and experimental work has been done to prove the selectivity of parts of a single nerve to explain this phenomenon (The Semon-Rosenbach Law). The conclusions reached by workers, although not conclusive, at least do present sufficient evidence to accept the Semon theory. This phenomenon is frequently observed by neurologists in their study of the pathology of the nervous system. The conclusions follow:

1. The nerve supply to the posticus abductors is poor.
2. The adductor musculature is considerably greater than the abductor, thus their greater resistance.
3. The fibers of the abductor muscle are said to lie in a separate bundle in the recurrent nerve.

4. Exposing nerves to low temperature by freezing interferes with the abductor function.

5. Following death, electrical irritability is found to cease first in the abductor muscles.

Sudden bilateral complete laryngeal paralysis brought about by a central lesion, such as hemorrhage, or by the accidental cutting of both nerves in thyroidectomy, embarrasses respiration because the cords fall medially. Cases have been reported of death by asphyxiation, but this is so rare that no case has appeared in the literature for several years. The usual lesion causing recurrent paralysis is peripheral, and, thus, probably unilateral. An early progressive bilateral lesion will embarrass respiration because of the contracting of the adductors. Later, when they are affected or paralyzed, breathing is easier.

Semon's law does not hold for functional paralysis so that we have a means of differentiating this nervous affection from an organic lesion. Aside from the usual etiological factors such as sex and emotional temperament, there is always an exciting cause such as sudden shock, operations, intense excitement or frustration. I have in mind a case history as follows:

Case History.—M. B., female, aged nineteen. She awakened with loss of voice (aphonia) after a tonsillectomy under ether narcosis, and for two years she was more or less hoarse. Apparently she had been a gifted singer, for her family were all musically inclined and she herself was a first soprano in a church choir at the time of her so-called "catastrophe." Recently two sisters had begun to appear in vaudeville. Her voice would be an asset to their act and she came to us in search of a cure and reassurance against recurrence.

It is understood, of course, that no operative procedure or operative accident in a tonsillectomy could by any means imaginable (short of cutting her neck) injure the laryngeal nerves. The patient must have had some psychogenic disturbance, and that her laryngeal dysphonia was functional was easily proved as follows: observation by indirect laryngoscopy showed an image in the mirror wherein on deep respiration the abductors moved laterally and were therefore normal. She could or would not phonate completely an "E, E, E" or "AH, AH" sound sufficiently to bring the cords together. Urged to make an extra effort, the cords would be seen almost to touch each other, but only for an instant, when they would immediately separate, as though weak or relaxed. This observation showed that the adductor muscles were involved but not organically, because a forced or voluntary cough was elicited. Coughing requires the cords to be closed so that sufficient pressure may be raised in the lungs to blast out a column of air, proving that our patient could adduct the vocal cords. The treatment of this case was psychologic; suffice to say, she is well now and sings over the radio.

Hoarseness is a very common symptom and frequent enough to excite interest. In order to find its cause one must polish up his head mirror and practice its use. One cannot see a larynx by only one glimpse of the vocal cords.

With constant practice, which comes with frequent laryngeal examinations, one trains one's head and neck muscles, and perfects a technic.

The laryngologist does not hesitate to cocainize a pharynx to stop the gag reflex. Neither will he neglect direct laryngoscopy which in the final analysis will substantiate an abnormal finding.

The first glimpse of a patient, his history and the general physical examination are important aids in diagnosis. Age, loss or gain of weight, duration of the hoarseness, its association with colds or sinus disease, etc., are all important. Examination of the chest may reveal pathology. Blood pressure readings will indicate the state of the arteries. Most significant of all, however, is the laryngeal picture.

An acute case of hoarseness may be associated with an upper respiratory infection as acute laryngitis. Hoarseness of longer duration may be a chronic inflammatory simple laryngitis. The laryngitis of venders and of news hawkers is of this type, the cords being thick and reddened and usually covered with exudate.

A vocal cord may be fixed and movement prevented by fixation or ankylosis of the crico-arytenoid articulation, due to arthritis or perichondritis of rheumatic origin, or arising from a streptococcus sore throat. Swelling of the tissue adjacent to the cords, due for instance to abscess, will also fix the cords.

The cause of dysphonia in laryngitis is the difficulty of the cords to vibrate normally. Fatigue of the muscle is produced, in turn inhibiting normal and complete cord closure and movements. Of three common diseases producing hoarseness, *i. e.*, tonsillitis, sinusitis and pharyngitis, the most usual cause for chronic laryngitis, aside from actual abuse of the voice, is sinusitis with its postnasal drip.

Chronic laryngitis due to alcohol or tobacco is occasionally seen. Restriction of their use, with constant observation of the larynx will soon prove the diagnosis.

The specific types of chronic laryngitis present in cancer, syphilis and tuberculosis are more common than is supposed. They must be thought of in all instances. The appearance of the lesion, its location and associated signs and symptoms will help the diagnosis. In syphilis and tuberculosis a Wassermann test, chest roentgenogram and an examination of the sputum are essential as positive aids. Cancer, however, particularly in its earliest stages, is not so specific. Biopsy, of course, may clarify the diagnosis.

In the great groups of benign growths that cause hoarseness, we find simple nodules or singer's nodes, fibromata, papillomata and angiomata. Long, pedunculated polypi may cause hoarseness and hide their presence by dipping into the trachea or into the ventricle, thus permitting the cords to approximate. Hematomata occur frequently.

Hoarseness, to recapitulate, occurs from interference with the movement of the vocal cords by any lesion which prevents the approximation and normal vibration of the cords. It is caused by interference with the motor nerve supply to the intrinsic muscles of the larynx, either wholly or in part, by lesions along the pathway of the laryngeal nerves and the fibers of that nerve in the vagus, from the medullary centers to the insertion of the superior and inferior laryngeal nerves into the intrinsic muscles of the larynx.

A functional type of hoarseness due to a psychogenic disturbance must be differentiated from hoarseness due to an organic lesion.

CLINIC OF DR. PHILIP COHEN

FROM THE PEDIATRIC SERVICE OF THE BRONX HOSPITAL

PRIMARY BRONCHOGENIC STAPHYLOCOCCIC PNEUMONIA

STAPHYLOCOCCIC pneumonia may be secondary to a focal infection, generally of the skin, or may be bronchogenic in nature, just as in the case of pneumococcus or streptococcus bronchopneumonia. Contrary to general belief, the latter is the more common variety. This is especially true in children. In the largest series on record, 312 cases, Chickering and Park,¹ in a military camp epidemic, described a clinical, respiratory, influenza-like disease, definitely not the picture of sepsis with secondary metastatic staphylococcic pulmonary foci. Their work showed that a positive blood culture does not necessarily indicate a secondary pneumonic process, for the abscess formation characteristic of staphylococcus pneumonia may result in the invasion of a pulmonary vein with consequent bacteremia. This occurred in about half of their cases. Thus bacteremia was the result of a primary staphylococcic pneumonia (akin to the bacteremia of pneumococcus lobar pneumonia). This was evidenced by the rarity of metastatic abscesses in other organs—bones, kidneys, spleen, skin, etc., which is the characteristic expression of staphylococcus sepsis.^{2, 3}

To distinguish between these two forms of pneumonia caused by the same organism, the term primary or bronchogenic staphylococcic pneumonia has been adopted for the non-septic form. Reimann,⁴ in a series of 6 cases, reported all the blood cultures negative. Kanof and Carnes's⁵ 13 cases of primary staphylococcic pneumonia were distinguished by negative blood cultures. Like Reimann, they found no metastatic foci in their primary cases, only in their secondary cases, which was part of the picture of staphylococcus sepsis. Thus it

seems that in contrast to true sepsis, in bronchogenic staphylococcus pneumonia the bacteria gain intermittent entrance into the blood stream and rarely in sufficient numbers to proliferate and to produce secondary foci.

Is this a rare disease? Is its occurrence unusual in children? Cole⁶ found the staphylococcus as a causative organism in 1.8 per cent of 1383 cases of the Rockefeller Institute. In 211 cases of bronchopneumonia⁶ he found 9 per cent due to *Staphylococcus aureus*. Chickering and Park¹ found the *Staphylococcus aureus* involved in 1.6 per cent of 800 pneumonia cases at the Rockefeller Institute. Netter⁷ reported 7.7 per cent of bronchopneumonia cases as due to *Staphylococcus aureus* and more recently Lyon⁸ found the *Staphylococcus aureus* in 9.6 per cent of 165 children ill with pneumonia. Habbe⁹ found the staphylococcus in 13 of 93 cases of bronchopneumonia, four times in 131 cases of lobar pneumonia, eight times in 20 cases of so-called "influenza pneumonia" and in 2 of 20 cases of postpertussis pneumonia. Menten, Bailey and DeBone¹⁰ in autopsy studies discovered the staphylococcus in 7 per cent of children dying of pneumonia, alone in 11 cases, and associated with other pathogenic bacteria in 65 of 131 cases. The highest occurrence was in infants. Seven of 89 infants under one year of age dying of pneumonia, yielded a pure culture of *Staphylococcus aureus*, and 50 out of 76 cases of pneumonia in this age group had a mixed culture. Kanof and Carnes⁵ also found the same predilection of the staphylococcus for the infant's lung. Considering the frequency of pneumonia, the incidence of the staphylococcus as etiologic factor in from 1.6 per cent to figures of 10 per cent or more in epidemics, shows that we are dealing with a common, not an unusual disease.

Analysis of the figures of all these authors reveals the affinity of this form of pneumonia for infants. The mortality rate is strikingly high and greatest for infants.

Bloomfield,¹¹ in studying the bacteriology of the noses and throats of healthy people in 1920 and 1921, found the *Staphylococcus aureus* an infrequent habitant. Later studies, however, stress the high incidence of *Staphylococcus aureus* in the nasal and pharyngeal flora. Park and Chickering,¹ in their studies, commented upon the frequent finding of this organism

in normal noses and throats. Shibley, Hanger, and Dochez¹² reported, in 1926, that 14 per cent of their normal group harbored the staphylococcus in their upper respiratory passages. In the presence of a cold, the incidence rose sharply to 40 per cent. McCartney¹³ (1928) observed and commented upon the not infrequent finding of the staphylococcus in the presence of nose and throat infections. Smith¹⁴ (1935), in his investigation of 16 normal infants in a healthy nursery, found 8 cases with positive staphylococcus nose and throat cultures, but the growth was scant. In 15 other healthy infants, in a nursery epidemic of staphylococcus respiratory diseases, 12 showed a throat culture in which the staphylococcus profusely predominated. In the 6 infants isolated for a cold in this nursery, all showed a heavy growth of staphylococcus from swabs of the upper respiratory passages. In a recent study of the relation of the upper respiratory to a rheumatic fever in children, Wheeler¹⁵ and his co-workers commented upon the surprising frequency of the *Staphylococcus aureus* in throat cultures. Like the Menten¹⁰ group, they came to the conclusion that the staphylococcus in recent years has become an increasingly frequent habitant in noses and throats of children. Twenty per cent of children showed the *Staphylococcus aureus* in routine nose and throat cultures during the summer, a period when respiratory infections are at their lowest ebb. In November and December, 70 per cent of these children had prolific growths of this organism from nose and throat cultures.

Kanof and Carnes⁵ pointed out that several of their cases of so-called "upper respiratory infection" exhibited *Staphylococcus aureus* in the blood stream. Viewed from a different angle, 76 per cent of *Staphylococcus aureus* cases had a preceding upper respiratory infection. *Staphylococcus sepsis* was not infrequently encountered in cervical adenitis cases of pharyngeal origin.

These reports emphasize that staphylococci are at times not only normally present in large numbers in the nose and throat, but, during the period of infection, often become the predominating organisms, sometimes in pure culture. The wave-like incidence of staphylococcus pulmonary infections and its propensity for infants in particular, has been pointed out.

As a result of a routine bacteriology examination of the sputum, throat swabs, and pleural exudates in children with pneumonia on the Bronx Hospital Pediatric Service 4 of the last 50 cases (8 per cent) were found by this author to have had the staphylococcus as the etiologic agent.

The clinical picture of staphylococcus pneumonia differs widely in infants and older children. Park and Chickering¹ described a clinical picture of septic temperature, profuse sweating, dusky cyanosis and a purulent sputum at times assuming a dirty salmon color or resembling anchovy sauce. In addition, the physical signs of pneumonitis were present. While leukocytosis was the rule, leukopenia was not infrequent. The course was extremely rapid with a distressingly high mortality rate, close to 100 per cent. It cannot be too strongly emphasized that this disease in adults is infrequently complicated by empyema. The occurrence of this ailment in a boy whom I recently treated and who was fortunate enough to recover showed these adult features. His history follows:

Case I.—Adult Form of Staphylococcus Pneumonia in a Boy of Twelve.—When I first saw L. S., an unusually well developed boy of twelve, on October 10, 1934, he gave a history of recurrent boils coupled with the inveterate habit of picking at his face and other regions where there were boils. Frequently after doing so the infected finger would be inserted in the nose with such vigor that at times epistaxis occurred. After a swim, a sport of which he was very fond, on October 9 he developed an apparently ordinary cold. Within twenty-four hours, however, the temperature rose to 103° F. and he began to cough. When I saw him he was breathing normally, but examination revealed mucopus in the left nostril, a red throat, and sibilant râles in both lungs. The temperature was too high for an ordinary bronchitis and I suspected incipient pneumonia.

By October 13 the temperature had risen to 104° F., the râles had assumed a subcrepitant character, and dusky cyanosis of the acral points had appeared. The diagnosis of pneumonia was becoming more obvious. The blood count on October 15 was:

Hemoglobin.....	86 per cent	Polynuclears..	67 per cent
Erythrocytes.....	5,600,000	Band forms..	9 "
Leukocytes.....	17,400	Lymphocytes....	22 "
Smear study.....	Normal	Eosinophiles....	1 "
		Monocytes....	1 "

The sputum had a distinctly purulent character and was so strikingly like the laudable pus of an evacuated boil that I had it cultured. The report (repeated and confirmed) was *Staphylococcus aureus*. At least 1 ounce of this unusual pussy sputum was raised daily and during all his illness this boy raised

at least 500 cc. The expectoration was never pink but had the exact yellow-green color and consistency of pure pus. Since both the sputum and the breath were odorless a fetid pulmonary suppuration was excluded. Septic fever and drenching sweats had begun and continued for four weeks. Prostration was not extreme, but an exuberant vitality was converted into profound weakness. The boy lost an average of 1 pound daily for twenty-five days.

The spleen was never palpable. Throughout the illness there were no boils, no paronychia, or any other signs of skin involvement, primary or secondary. The left nostril which was filled with pus on my first visit unfortunately had been cleaned out continually, but a smear taken at the time of the sputum

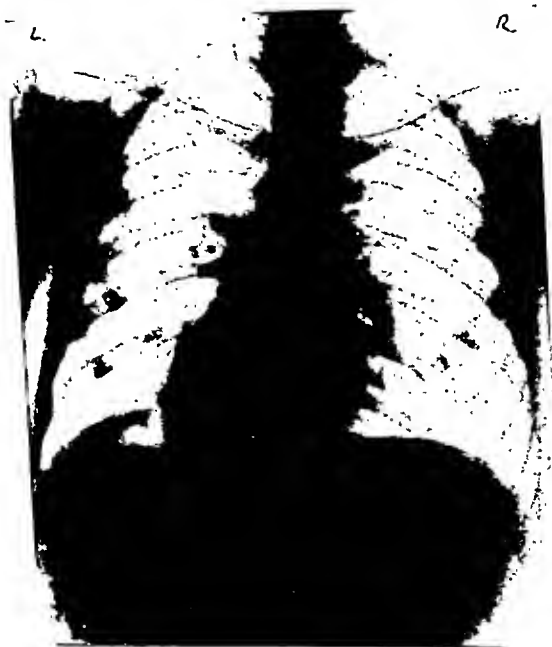


Fig. 156—Case 1. L. S., twelve years, 10/18/34. Soft hazy infiltrations in both lower lobes. Left somewhat obscured by the heart shadow.

culture showed gram-positive cocci predominating. The urine was always negative. There was nothing in the clinical course to suggest sepsis.

On October 18 signs of consolidation appeared in the left lower lobe with numerous rales at the right base. On the 21st, in the left lower lobe, I detected pectoriloquy and whispering pectoriloquy which, in addition to metallic rales suggested cavitation, a far more common complication in the adult type of staphylococcus pneumonia, according to Reimann,⁴ than empyema. Bedside roentgen examination (Fig. 156), however, showed no cavitation though revealing consolidation and probable abscesses. The heart sounds were rapid and muffled, the pulse dicrotic and the boy appeared very toxic. Large doses of sodium and luminal failed to control his cough. With the advent of poor

myocardial action, digitalis was started. The raising of purulent expectoration now reached its height (2 ounces daily) and probable swallowing of some of this sputum with its attending nausea made him vomit. Dusky cyanosis continued throughout the illness but was never severe enough to require oxygen therapy.

On October 22 he began to eat better and on the 24th the blood count showed:

Hemoglobin.....	86 per cent	Polynuclears.....	72 per cent
Erythrocytes.....	5,600,000	Band forms.....	12 "
Leukocytes.....	29,500	Lymphocytes.....	15 "
		Eosinophiles.....	1 "

On October 25 he developed the prolonged expiratory wheeze characteristic of asthma, with sibilant and sonorous râles in both lungs, lasting forty-



Fig. 157.—Case I. 10 29 34. The entire right lung is now studded with small hazy infiltrations. There is some consolidation and pleural thickening of the right lower lobe. The left lung shows some increase in number and density of previous shadows.

eight hours. This came on about the time when consolidation of the right lung was detected on physical examination. At the same time he complained of pain in the left chest, but there were no signs of pleural involvement. I feared rupture of an abscess into the pleural cavity. Exhausting coughing spells

continued with occasional vomiting, but the patient ate remarkably well, ingesting a high caloric diet. Codeine in doses of 1 grain every three hours had no effect on either the pain or the cough. After two days the chest pain subsided and the increased dusky cyanosis abated slightly. The roentgen findings are shown in Fig. 157.

On October 30, a second attack of asthma occurred, confined, curiously enough, to the right lung where there was diffuse involvement. The left lung had chiefly the basal part affected. The next day there was blood in the sputum. On November 1 the signs of consolidation of the left lung had largely disappeared, but there were still numerous râles throughout the right lung. The right lower lobe, in addition to consolidation, now had signs suspicious of cavi-

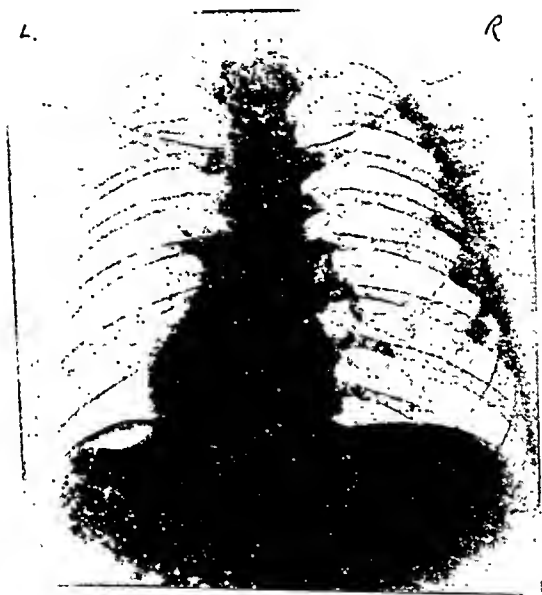


FIG. 158. Case I. 12 4 34. Both lungs normal now except for generalized increase of lung markings.

tation, with pectoriloquy and tinkling râles, not verified by roentgen examination. That night the patient suffered from excruciating pain in the right axilla, and once more I feared pleural invasion.

Having observed that the spread of physical signs and asthmatic attacks usually followed close upon violent coughing spells, I began to visualize a bronchogenic spread and therefore deemed it of the utmost importance to stop the cough with its deleterious consequences.

So for the next three days I kept the patient in bed under the influence of morphine in large doses. The cough gradually ceased, and the pain in the chest diminished and disappeared entirely in two days. The expectoration ceased and the fever declined, but the cyanosis and perspiration continued. Exhaustion became extreme either coincidentally or as a result of the mor-

phine therapy; I am inclined to believe that there was causal relationship between it and the morphine therapy. On November 5 the temperature became normal, four weeks after onset of the illness. He still coughed, but relatively little. The expectoration had become increasingly smaller but the drenching sweats persisted. The patient was too exhausted to react or eat as well as when more acutely ill. Fortunately, however, during the next three weeks the physical signs cleared up and he began slowly to improve. On December 4 he was able to go out and have an x-ray of his chest taken, which proved to be almost normal (Fig. 158). Further examination on January 14, 1935, revealed essentially normal radiographic findings.

Comment.—We have in this case a form of primary bronchogenic staphylococcus pneumonia which may be termed the adult type, characterized by breaking down of lung tissue, as evidenced by the large amount of pus coughed up during illness. We witnessed extreme toxemia, profound prostration, septic temperature (no manifestation of sepsis), drenching sweats, dusky cyanosis and the recovery in pure culture of *Staphylococcus aureus* from the purulent sputum. Signs of consolidation with pectoriloquy and whispering pectoriloquy indicated a destruction or necrosis of pulmonary tissue of large dimensions, despite the negative roentgen findings for cavitation. The bacteriological studies, the apturid character of the sputum and lack of fetid odor to the breath excluded anaerobic necrosis of the lung. At no time was there marked anaerobic or much increase of respiration in the presence of cyanosis.

How did the patient contract this disease?

With his habit of picking on his skin which evidently harbored numerous staphylococci, and then his nostrils, he probably made a rich transplantation to the nares. On my first visit, as stated, the left nostril was full of pus which later showed a predominance of gram-positive cocci. Then, the factor of infection of the respiratory tract allowed the staphylococcus to travel down the bronchial tubes to the lungs.^{12, 13, 14, 15} In spite of two attacks of pleural pain, indicating subpleural foci, no empyema or pyopneumothorax developed, a striking feature of the adult form of primary staphylococcus pneumonia. For the reason that the liberal use of morphine may have been instrumental in avoiding such an undesirable complication and to minimize the bronchogenic spread as a result of the distressing cough, I advocate the judicious use of morphine in this pulmonary syndrome.

Very interesting as a by-product, were the asthmatic attacks. We speak glibly of bacterial allergy, yet this boy had one attack of asthma involving both lungs and later two attacks confined to the right lung where the lesions were more diffuse and more numerous, bringing up an interesting speculation regarding local or general sensitization.

Because this boy was so presumably subject to staphylococcus infection and sensitive to the staphylococcus protein, skin tests were performed with a staphylococcus vaccine and a staphylococcus toxoid in low dilutions. The reactions to both were markedly positive. He was then inoculated with both the toxoid and the vaccine in dilutions of increasing concentration until skin reactions to both became negative. This therapy, which consumed six weeks at the rate of 2 injections weekly, was adopted because of the good results reported by various observers.^{16, 17} In September, 1935, he was still negative to intracutaneous tests with both toxoid and vaccine. Since this treatment, he has been free of boils, has had no asthmatic attacks and has been in excellent health. I have had no experience with the new staphylococcus antitoxin, and cannot say whether it should be used for staphylococcus pneumonia, but it may be worthy of trial in view of reports.^{18, 19}

Primary Staphylococcus Pneumonia in the Infant.—

The picture of primary staphylococcus pneumonia in the infant is quite different from that of the adult, just described, particularly with regard to speedy susceptibility to pleural complications. The explanation may be that the older child or adult has a greater margin of safety because the suppuration in this primary bronchogenic form begins in the terminal bronchioles with ample pulmonary tissue intervening between the bronchiolar focus and the pleura. The infant's lungs are much smaller than those of an older child or adult, but, unfortunately, the furuncles are not. The natural progression of a lung boil, therefore, quickly effects penetration into the pleural cavity. If a continuous tract is laid open between the small bronchus and the pleura a pyopneumothorax results. If the abscess simply perforates into the pleura without continuity with the bronchial end, simple empyema eventuates. The respiratory infection shortly develops into a rapidly spreading and very toxic pneumonitis which in a day or two under-

goes the catastrophe of a parapneumonic empyema or a pyopneumothorax. There is a marked and sudden change when this occurs. The infant becomes very cyanotic and dyspneic—not the dusky or cherry-colored cyanosis described for the older child's staphylococcus pneumonia, but the indigo type necessitating immediate oxygen therapy. The rapid changes and picture of extreme shock with anoxemia (from pleural involvement) are practically diagnostic of this form of infantile pneumonia.

In a few cases, the pneumonitis is so violent with many confluent suppurative and necrotic pulmonary foci, that the infant dies within a day or two, even before pleural complications can supervene.^{10, 14} The vast majority, however, progress into an acute empyema or pyopneumothorax. The following 2 cases illustrate this characteristic clinical picture of primary staphylococcus pneumonia in infants, one developing empyema and the other pyopneumothorax.

Case II.—L. S., a first child, thirteen days old, born to parents healthy and free of familial disease, was admitted to the Bronx Hospital, January 22, 1935. She was a full-term baby, low forceps delivery, and was normal after birth until five days of age when she presented evidence of a cold with snuffles and sneezing. Five days later she was taken home and the following day had a little fever, coughed and vomited. During the next twenty-four hours her temperature rose to 102° F. and I was called to see her.

Upon examination I found a red throat, rhinitis, slight dullness at the left base, no change in breath sounds, and marked distention of the abdomen. The next day (thirteen days of age) her temperature rose to 103° F., she became more distended, began to refuse her bottle and was slightly cyanotic. She was breathing rapidly (50 per minute) and in addition to dullness had diminished breathing at the left base. She was rushed to the hospital. Immediately after admission she stopped breathing, turned cyanotic, and was on the verge of exitus. An alert intern quickly gave her artificial respiration, and as soon as she began to breathe put her into an oxygen tent.

On January 23, when she was two weeks old, I found her to be cyanotic with grunting and respiring rapidly (60 per minute), despite the fact that she was in an oxygen tent. I also noted dullness and diminished bronchial breathing at the left base with an occasional fine r  le. The urine was negative except for a few white cells. There were no furuncles, no skin infections and no paronychia. The blood count at this time was:

Hemoglobin.....	80 per cent	Immature polys.....	25 per cent
Erythrocytes.....	4,500,000	Lymphocytes.....	8 “
Leukocytes.....	73,300	Monocytes.....	18 “
Mature polys.....	47 per cent	Turck cells.....	2 “

Marked toxic granulations of the neutrophils were noted

January 24: Dulness increased to involve the upper lobe. The lower lobe was rather flat on percussion, suggesting fluid, and diminished bronchial breathing was still heard. This occurred only two days after signs of pneumonia were found.

January 25: Flatness now completely replaced by dulness, indicating, I thought, fluid in the left pleura.

January 26: Roentgen examination (Fig. 159) showed consolidation of the left lung with displacement of the mediastinum to the left, the side of the



FIG. 159. Case II. 1 26, 35. x-Ray shows consolidation of the left lung with the mediastinum displaced to the left, the side of the lesion, suggesting atelectasis. Right lung was emphysematous. Fluid, in left chest, proved by aspiration.

lesion suggesting atelectasis. Right lung emphysematous. Whether there was fluid or not could not be stated by roentgenologist. I aspirated the chest just below the angle of the left scapula and removed 50 cc. of thick, green, cheesy pus. This pus was so thick that the Potain method of aspiration was unsuccessful and the syringe method was substituted. The culture of the pleural pus was *Staphylococcus aureus* on three occasions. The general condition improved so much after aspiration, especially the cyanosis, that we were able to dispense with the oxygen tent. The baby was then seventeen days old.

January 28. At the region of the first aspiration there was a boil-like

infection. Signs of fluid were still present and I aspirated 40 cc. of thick pus, allowing air to enter the pleura after the syringe was disconnected until the pus stopped oozing. A wet dressing was applied to the chest wall.

January 29: Roentgenographic examination showed cloudiness over the left chest, probably due to the thickened pleura and residual fluid. The introduced air had displaced the mediastinum slightly to the right (Fig. 160). The baby, now twenty days old, showed dullness over the left lower lobe and flatness over the upper lobe. Aspiration above the angle of the scapula pointing the needle upward netted 35 cc. of green pus, liquid now instead of cheese—



Fig. 160.—Case II. 1/29/35. x-Ray now shows cloudiness over the left chest, due to residual fluid and thickened pleura.

since the air replacement was begun. As after the previous aspirations, a boil formed at the site of puncture.

January 31: Pus was streaming through the last puncture wound. Pressure over the side of the chest caused more pus to exude and coughing resulted in an expulsive stream. About 4 ounces of pus drained daily by this method, far more than infiltration of the chest wall could account for. Bubbles argued for an intrapleural origin. In other words we were virtually dealing with a traumatic empyema necessitatis. Alcohol dressings were applied to the chest.

February 2: Spontaneous drainage through the puncture site had stopped and there was still dullness of the upper lobe. A needle was inserted which

dropped as if into a cavity. Ten cc. of liquid pus was withdrawn. The temperature, which had ranged from 100° to 103.6° F. had come down to normal.

February 4: Twenty cc. of thick pus evacuated from left upper lobe area.

February 7: A sixth aspiration resulted in the removal of 20 cc. of thick pus. Temperature continued normal, the child was eating well and holding her weight. Roentgen examination showed consolidation of the lower two thirds of the left lung. There was a large pneumothorax from air replacement on this



Fig. 161—Case II. 2/7/35. x-Ray shows consolidation of the lower two thirds of the left lung. There was a large pneumothorax on this side from the air introduced after aspiration. This caused displacement of the heart and mediastinum to the right. There was a little fluid present yet, but a marked soft tissue swelling is visible over the left chest.

side which displaced the heart to the right. There was little fluid present, but a marked soft tissue swelling was visible over the left chest (Fig. 161).

February 8: A rise in temperature to 101.8° F., dulness of the upper lobe and almost absent breathing. Although not certain that fluid was present, I inserted a needle for the seventh and last time. Nothing was obtained.

In all 175 cc. of pus had been aspirated and 150 cc. had drained spontaneously through the third puncture wound. The actual cure by aspiration occupied a period of only nine days. The total cure occupied but two weeks, remarkable for a cure of genuine empyema thoracis. This is in contrast to

statements made as to the longer duration and fatal procrastination of the aspiration treatment of empyema,^{25, 32, 33}

February 14: Temperature normal since February 8. Dulness over the upper lobe, slight dulness over the lower lobe, fine râles scattered throughout. The infiltration of the subcutaneous tissue was rapidly subsiding. Roentgenogram showed marked resolution of the process in the left chest. There was a resolving pneumonia at the base. The ribs in the axillary line showed slight periosteal thickening and the left chest was narrow compared to the right.



Fig. 162.—Case II. 2/23/35. x-Ray shows further clearing of the process in the left chest. There was still thickening of the pleura and periosteum of some ribs. It was now evident that the consolidation of the left lung was resolving.

The soft tissue swelling was much diminished. In order better to expand the lung, CO₂ inhalations were attempted, but the child struggled so violently that this was soon abandoned.

February 23: Left chest still dull. Râles present. Breathing diminished but less marked than before. The child looked well and was gaining weight. Roentgenogram showed further clearing of the process in the left chest. There was still thickening of the pleura and also of the periosteum of some ribs. It was now evident that there was consolidation of the left lower lobe which was resolving (Fig. 162).



Fig. 163—Case II. 5 7 35. x-Ray now shows no abnormality of the lungs, but a thickened left pleura as the residuum of the empyema.



Fig. 164.

The weight on admission, January 22, was 8 pounds. On March 1, when discharged she weighed 8 pounds 10 ounces. Examination in April showed slight dulness and a loss of elasticity of the left chest wall, but the breath sounds were normal and there were no râles. Roentgenographically there was still clouding of the left lung and a slight thickening of the pleura.

Roentgen examination in May (Fig. 163) showed no abnormality of the lungs, but a thickened pleura, a residuum of the empyema. The patient is now almost one year of age and weighs 23 pounds, has excellent color, presents a normal examination with equal expansion of both lungs and no deformity of the chest (Fig. 164).

Comment.—This case began with apparently an ordinary respiratory infection. After a few days, when the baby was twelve days of age, pneumonia probably set in; two days later signs of fluid were present, corroborated by the roentgen examination and proved by aspiration. That the staphylococcus pneumonia developed through the bronchogenic route was demonstrated by the absence of history or findings of a skin infection in the mother or child, and by the course.

I agree with those who feel that empyema rarely if ever needs immediate surgical intervention.^{21, 22, 23, 24, 25, 26} Certainly the results of large series of cases treated with aspiration with or without air replacement compare favorably with the results obtained by surgery.^{21, 22, 23} In my experience operation on empyemas in babies below three months of age is practically an invariably fatal procedure.

I have found aspiration with air replacement more effective than simple aspiration. In the first place, it is easier to empty the pleural cavity. Secondly, the pleural layers are better cushioned, and, even more important, thick, cheesy pus, such as was aspirated in this case, is liquefied by the entrance of air facilitating further aspirations.

If aspiration fails, in a short time, to evacuate the chest and relieve the tension of the mediastinum, closed thoracotomy is indicated. The criteria for this operation are: persistent signs of fluid, dyspnea, and the roentgen finding of a displaced mediastinum.

In the past two years we have subjected 3 infants to a closed operation with excellent recovery in all, confirmed by roentgen studies which demonstrated satisfactory emptying of the involved chest. The temperature may remain somewhat elevated after good drainage is established for the reason that

the underlying staphylococcus pneumonia usually runs a course of from three to six weeks, after which recovery ensues.

The staphylococcus, like the pneumococcus and the streptococcus, is composed of different strains. The toxicity of the invading strain is an important factor in the prognosis of the staphylococcus pneumonia. The smooth strains are not only distinguished by different carbohydrate fractions, but are better toxin producers.^{35, 36, 37} The variation in toxin elaboration has been known for some years.^{16, 17, 18, 35, 37} The staphylococcus toxin or toxins have a necrotizing effect on the skin and subcutaneous and muscular tissues, hemolyze red blood cells, and, when injected intravenously, produce death in animals. There is a high correlation between these various effects so that the toxin can be titrated according to its hemolytic powers.^{16, 17, 18, 36, 37} Therefore, a *Staphylococcus aureus* grown on blood agar plates which has no zone of hemolysis probably belongs to one of the less potent strains.

Another recently discovered curious fact about the staphylococcus is that the toxic strains produce colonies not of the classic golden color, but of a lighter yellow.^{35, 39} In this case and in the first patient, the boy of twelve, the organism cultured was not hemolytic and of a golden color. Apparently this less toxic strain played an important rôle in the successful outcome of these 2 cases. In Case III, soon to be described, there was recovered a staphylococcus which was both yellow and hemolytic, and termination was fatal.

Since staphylococcus pneumonia in infants is almost always accompanied by empyema or pyopneumothorax, a good index of the frequency of this form of pneumonia can be obtained by statistics of the frequency of staphylococcus empyema in children. Holt and Howland²⁷ report an 8 per cent incidence of staphylococcus empyema in children, which is the percentage reported from the Brooklyn Jewish Hospital.²⁸ Wilensky²⁴ reports 10 per cent.

When the age group is very young the incidence rises. In children below two years of age, Spence²⁹ reported 19 per cent; Heuer³⁰ 22 per cent; Rienhoff and Davison³¹ 20 per cent; Hart²⁶ 18 per cent. and Neuhof and Berck³² 22½ per cent.

In infants under one year of age the incidence rises almost to 55 per cent; below six months of age to 71 per cent.

I believe it is correct to say that the most common cause of empyema in an infant below three or even six months of age is the *Staphylococcus aureus*.^{20, 29, 32} Neuhof and Berck do not clearly separate the primary from secondary or septic forms, as the result of which the picture of sepsis in their cases is more prominent and much more frequent than in the primary form. Yet most of the postmortem studies of their cases proved that the children died not of sepsis but of a continued pneumonic infection with pleural suppuration, which finally eventuated into a fatal pericarditis, a dreaded complication of left-sided empyema. The mortality of staphylococcus empyema in infants is between 50 and 100 per cent,^{20, 21, 29, 30, 32} probably nearer the latter figure in very young infants.

Case III.—R. F., a female, seven weeks of age, was admitted to the hospital with a history of having developed a cold seven days before admission that began with a running nose, and a slight cough. Four days later the temperature was considerably elevated and on the fifth day rose to 103° F. The child began to cry and was restless. On examination by Dr. N. Ravin, signs were detected in the right upper lobe. The next day the child was worse and I was asked to see her. Examination revealed spread of the process on the right side and an incipient pneumonia on the left side. There were no lesions of any kind on the skin and no one in the family was suffering from boils or any other skin infection. The rest of the examination was negative except for a slight cyanosis and a distended abdomen which is a prominent feature of staphylococcus pneumonia in infants, and frequently simulates peritonitis. My attention has been called to one case in a newborn infant where this mistake in diagnosis was made and the child was operated on for peritonitis. At autopsy pneumonia and empyema were found due to staphylococcus aureus.

On the following day, the seventh of her illness, the baby became suddenly so much worse that she was sent at once to the hospital.

On admission she was acutely ill, moderately cyanotic, very restless, cried loudly and was suffering from rapid labored respiration. There was consolidation of most of the right lung with numerous subcrepitant râles throughout. In the left lung there was a mixture of sibilant, sonorous and subcrepitant râles, with an area of dullness and bronchial breathing in the left axillary region. There was slight cervical rigidity, but the fontanelle was normal. The abdomen was greatly distended.

The findings of a roentgen examination explained the sudden change in this child's condition. There was marked consolidation throughout the right lung with a small pneumothorax in the right axillary region. The mediastinum was displaced to the left. This was interpreted as being due to a mixture of air and fluid in the pleural cavity in addition to pneumonia on the right side (Fig. 165).

The blood count showed:

Hemoglobin.....	62 per cent	Lymphocytes.....	18 per cent
Erythrocytes.....	4,500,000	Monocytes.....	8 "
Leukocytes.....	24,500	Metamyelocytes.....	3 "
Polys.....	15 per cent	Band forms.....	56 "

We now felt that we were dealing with a staphylococcus pneumonia in an infant, with perforation of an abscess, and a resulting pyopneumothorax. Aspiration in the right axillary region yielded 15 cc. of milky fluid with a reddish tinge such as Chickering and Park¹ described as characteristic of the sputum of their cases. In addition, 50 cc. of air was aspirated. The child was then put into an oxygen tent, but in spite of two more aspirations with removal of air and 10 cc. of thin fluid each time, her condition grew worse.



Fig. 165. Case III. 5-6-35. x-Ray showed a marked consolidation throughout the right lung, with a small pneumothorax in the right axillary region. The mediastinum was displaced to the left. The picture was that of pneumonia of the right side with a mixture of air and fluid in the right pleura.

Cyanosis and dyspnea progressively increased and the marked abdominal distention persisted until four days after admission when the child collapsed with subnormal temperature, shallow decreased respirations, and died.

Culture of the pleural exudate revealed a mixture of pneumococci and staphylococci; the latter growing in colonies of a color a shade deeper than ordinary yellow and distinctly lighter than the classic gold, apparently of a toxic strain. Culture terminated 16-18-20-27.

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CLINIC OF DR. J. EPSTEIN

STUYVESANT POLYCLINIC

FURTHER CLINICAL OBSERVATIONS ON THE TREATMENT OF PERTUSSIS WITH GOLD TRIBROMIDE

PERTUSSIS or whooping cough is a world-wide disease and has been known for many centuries. It is almost always present in an epidemic, endemic or sporadic form. There are seasonal and yearly fluctuations in the morbidity, complications and mortality. Whooping cough is more prevalent in the southern states and more severe in the northern states. The higher morbidity in the southern states is probably due to the greater susceptibility of the negro population to whooping cough. The higher mortality in the northern states is due to the greater incidence and severity of the respiratory diseases in the cold climate. The negro race living in the northern states has both a greater morbidity and a greater mortality from pertussis than the white race. The disease affects chiefly young children, though no age is exempt. The younger the child, the worse the disease and the greater the mortality. The annual mortality from pertussis in the registration area of the United States during recent years has been about 10,000. The universal occurrence of pertussis, the long duration of the illness, the debilitating effect on the child, the many complications and the high mortality make this a dreaded disease.

Gold tribromide was practically unknown in the field of medicine until the year 1930. In that year, I became interested in the medicinal value of gold tribromide and have made many observations on its pharmacology and therapeutics. I was led to the study of gold tribromide through two different but convergent fields of interest. One was through the study of the various bromides and the other through a search for some reliable remedy in the treatment of whooping cough. In the

study of the bromides, I divided them on a chemical basis into monobromides, dibromides and tribromides. Potassium bromide (KBr), sodium bromide (NaBr), lithium bromide (LiBr), and ammonium bromide (NH₄Br), are monobromides. Calcium bromide (CaBr₂) and strontium bromide (SrBr₂) are dibromides. Gold bromide (AuBr₃), arsenic bromide (AsBr₃), iron bromide (FeBr₃) and aluminum bromide (AlBr₃) are tribromides. In observing the action of the bromides, I found that the dibromides gave better bromine or sedative action than the monobromides and that the tribromides were more effective than the monobromides or the dibromides. Of the tribromides, the most suitable preparation for medicinal purposes is gold tribromide. This drug I have used in whooping cough with very good results. In MEDICAL CLINICS OF NORTH AMERICA, July, 1933, I stated: "The result of the treatment with gold tribromide in about seventy-five whooping cough cases from my own practice and from other observers was most gratifying. After two or three days of treatment, the cough was less frequent, the attacks were shorter and milder and the children slept better. In three or four weeks, the cough gradually ceased."

Further Clinical Observations.—Since my previous report on the treatment of pertussis with gold tribromide, a large clinical experience has accumulated showing the undoubted value of this gold salt. Of the large number of whooping cough children who were successfully treated with gold tribromide, a brief report is given here of 350 cases.

Report of 350 Whooping Cough Cases.—During a period of almost six years, 350 whooping cough cases received special study. There were 191 female and 159 male children; their ages ranging from three weeks to eight and one-half years. To 20 of the 350 children, prophylactic vaccination was given by the family physician from one to two years prior to the onset of the whooping cough. The 350 children were divided into two groups: those who were treated with gold tribromide exclusively and those who were treated with other therapeutic measures.

Gold Tribromide Treatment.—To 250 children gold tribromide was given as the only medication. The results of this treatment may be summarized as follows: There was con-

siderable improvement in the cough within a week and it entirely subsided in 100 children by the end of three weeks; in 75, by the end of four weeks; in 45, by the end of four and one-half weeks and in 30, by the end of five weeks. The average duration of the illness in the 250 children who were treated with gold tribromide exclusively was three and eight-tenths weeks.

Drug, Vaccine and Placebo Treatment.—In order to have a comprehensive idea of the therapeutic value of gold tribromide in the treatment of pertussis and to compare the gold treatment with other methods of treatment, 100 whooping cough children were used as controls. Fifty-five of these 100 children were treated with the usual antiwhooping cough remedies consisting chiefly of sodium bromide, antipyrine, phenobarbital and camphorated tincture of opium. Twenty-five children were treated with pertussis vaccine. Twenty children received no medication at all but were given various placebos consisting mainly of water flavored and colored with different syrups.

The results with these various treatments are briefly as follows: Improvement in the cough was not noticed until the beginning of the third week and the average duration of the illness in the 55 drug-treated children was nine weeks; in the 25 vaccine-treated, was ten and six-tenths weeks and in the 20 placebo-treated, was twelve weeks. The average duration of the illness in the entire group of 100 children who were treated with drugs, vaccines or placebos was ten weeks.

In this group of 100 children were included the 20 children who received prophylactic vaccination. The prophylactic treatment in these 20 cases did not have any material effect on the course of the disease. In my own practice, I found the preventive vaccination of pertussis of doubtful value.

Conclusion.—From a comparison of the therapeutic results in the gold tribromide treated children with those treated by other methods, it is clearly evident that gold tribromide is of decided therapeutic value in the treatment of whooping cough. Under the gold treatment the average duration of the cough in 250 cases was three and eight-tenths weeks, while under the drug, vaccine and placebo treatments, the average duration of the cough in 100 cases was ten weeks. A glance at the figures

will clearly show that under the gold treatment the duration of the whooping cough was cut down almost to one-third. It has also been of great help in relieving the violence and the frequency of the coughing seizures and in giving the children considerable rest and sleep.

Gold Tribromide in the Treatment of Other Cough Disorders.—Clinical experience has shown that gold tribromide is also of considerable benefit in relieving the cough due to any irritation along the respiratory tract especially when the cough is persistent and spasmodic. In a special study of 50 children during the winters of 1935 and 1936 who were affected with various cough disorders, gold tribromide was found far superior to the usual cough remedies. I have used this gold salt in a considerable number of cases of bronchitis and bronchial asthma and found it to cause relaxation of the spasms with great relief in the cough and dyspnea. A great many physicians and phthisiologists are using gold tribromide for the relief of the cough due to pulmonary tuberculosis. It is claimed that gold has a specific effect on the tuberculous process. Gold tribromide is preferable to gold and sodium thiosulfate in the treatment of pulmonary tuberculosis because it is given by mouth thus avoiding the trials and tribulations of intravenous medication.

Gold Tribromide in Medicine.—The therapeutic value of gold tribromide is due to the effect of the gold ions and the tribromine ions. Gold is an antiseptic and may have a selective inhibitory action on the Bordet-Gengou bacilli. It is also said to be a stimulant to the defensive processes of the body similar to nonspecific proteins. The tribromide has a sedative action on the nervous system including the coughing center. No other gold salt and no other bromide salt has the same pharmacologic action and therapeutic effect in pertussis as gold tribromide.

Pharmaceutical Preparation of Gold Tribromide.—As gold tribromide is an unstable and easily oxidized chemical, it undergoes deterioration and decompensation when dispensed in pills, capsules or in an aqueous solution. It was therefore found difficult to make it in a reliable, standardized preparation. After considerable experimenting, it was finally made up in a stable, assayed and palatable elixir known pharmaceu-

tically as elixir bromaurate. The average dosage for children of this elixir is 1 teaspoonful every four hours. Adult's dosage is 2 teaspoonfuls.

Summary.—Three hundred and fifty whooping cough cases are reported. To 250 gold tribromide, in the form of elixir bromaurate, was given exclusively and the average duration of the illness was three and eight-tenths weeks. To the other 100, various drugs, vaccine or flavored water was given and the average duration of the illness was ten weeks. It is therefore clearly evident that under the gold treatment the duration of the illness was greatly shortened and there was an almost immediate improvement in the cough and in the general condition.

The pharmacologic action and the therapeutic effect of gold tribromide indicate its usefulness not only in whooping cough but also in other cough disorders and in bronchitis and bronchial asthma. Aurotherapy is giving encouraging results in the treatment of pulmonary tuberculosis especially in relieving the cough.

GOLD AND SODIUM TETRABROMIDE IN THE TREATMENT OF EPILEPSY

IN an effort to interpret chemical valences into terms of medicinal values, I classified the bromides into monobromides, dibromides and tribromides. Starting with the assumption, later proved by clinical experience, that there is an increase in the therapeutic effect of the bromides with an increase in their valences, I came to the study of gold tribromide (AuBr_3) which is now being used extensively in the treatment of pertussis.

Encouraged with the therapeutic results of gold tribromide in the treatment of pertussis, I began about three years ago a study of gold and sodium tetrabromide (AuNaBr_4) in the treatment of epilepsy. Though pertussis and epilepsy are two distinct and separate diseases, they have many points in common. Both are characterized by spasmodic or convulsive seizures or fits and both have a sudden onset and a sudden termination. Both diseases are commonly set off by some reflex irritation and in both conditions there is a general nervous hyperirritability. Both pertussis and epilepsy are benefited by sedative drugs especially the bromides. Bearing in mind the certain similarities of these two diseases and the fact that the spasms of pertussis are effectively controlled by a tribromide of gold, it was reasonable to assume that a tetrabromide of gold would aid in controlling the spasms and convulsions of epilepsy. I therefore tried gold and sodium tetrabromide in the treatment of epilepsy.

Gold and Sodium Tetrabromide.—This chemical was hardly known in medicine before I became interested in its therapeutic possibilities in the treatment of epilepsy. It is a dark brown crystalline powder, soluble in water and unstable when not properly dispensed.

The exact effect of gold on the nervous system is hard to determine. Gold is claimed to cause absorption of inflammatory and edematous nerve tissue. The effects of the bromides

on the nervous system are well known; they act as neurosedatives and cerebral depressants. The exact action of the sodium in this chemical cannot be definitely stated. The therapeutic value of the compound of gold and sodium tetrabromide cannot be readily interpreted because the amount of bromide in the usual dosage of gold and sodium tetrabromide is in itself too small to cause a marked neurosedative effect. It must, therefore, be assumed that as a result of the chemical changes and reactions taking place between gold, sodium and bromine, a new chemical is formed which has definite anti-convulsive, antispasmodic and neurosedative action. The therapeutic effect of a tetrabromide has been shown to be greater than that of a tribromide, dibromide or monobromide.

Gold and Sodium Tetrabromide in the Treatment of Epilepsy.—After considerable pharmacologic and therapeutic tests with gold and sodium tetrabromide, I tried it in 35 cases of epilepsy. Of these 35 cases, 25 were grand mal and 10 petit mal. Many of these patients came from the practice of other physicians to whom I wish to express my appreciation. The 35 cases were under observation for two years. The method of treatment was as follows: For the first six months, they were given gold and sodium tetrabromide exclusively; for the second six months, they were given sodium bromide, phenobarbital and occasionally other sedatives; for the third six months, they were again treated with gold and sodium tetrabromide exclusively; for the fourth six months, sodium bromide, phenobarbital and hyoscyamus were given. The results were definitely in favor of the gold treatment. During the two six-month periods when they received gold and sodium tetrabromide exclusively, the duration of the convulsive attacks was shortened; the severity of the spasms was diminished and the periods between the epileptic seizures were lengthened.

While the number of cases observed were too small and the time too limited for a full estimate of the therapeutic value of this gold salt, still it has shown definite therapeutic action and is worthy of further trial and larger clinical experience. When one considers the poor results with the usual remedies in the treatment of epilepsy, this new chemical will, after a fair trial, be shown to be superior to the present drug treatment. The small amount of bromide in gold and sodium

tetrabromide will not cause the deleterious effects so common with the large doses of sodium or potassium bromide or phenobarbital.

Gold and Sodium Tetrabromide in Other Diseases.—

The therapeutic effect of this gold salt in epilepsy has suggested its use in allied diseases. I have used this chemical in a few cases of migraine, paralysis agitans, chorea and the neuroses with encouraging results.

Pharmaceutical Preparation.—Gold and sodium tetrabromide should not be used in pills, capsules or tablets but in a properly prepared solution. A uniform, standardized preparation of gold and sodium tetrabromide is now available. It is known pharmaceutically as aurosodobrom. The dosage for adults is 10 drops; for children, 5 drops in water three or four times a day after meals or more often when indicated.

Summary.—While my experience with gold and sodium tetrabromide in the treatment of epilepsy has not been extensive, it has already given sufficient evidence of its undoubted value. Gold and sodium tetrabromide has the therapeutic effect of gold and tetrabromine. It acts as an effective anti-convulsive, antispasmodic and neurosedative.

CLINIC OF DR. CHARLES A. POINDEXTER

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EVALUATION OF THE CARDIAC STATUS OF THE SURGICAL PATIENT

THE successful outcome of an operative procedure to relieve a surgical condition in a patient who has also a damaged heart requires more than a mere delineation of cardiac diagnosis. The problem requisitions the skill and judgment of the internist, the surgeon and the anesthetist in order to conquer the condition needing surgical interference as well as to allay the fear and anxiety of the patient.

The fear and anxiety that accompanies the problem of determining the surgical potentialities of a cardiac patient continues because of the general fear of heart disease and because of the often repeated difficulty of distinguishing surgical shock from primary cardiac failure. Postoperative heart failure has long been an old "hold-all" into which has poured unfortunate failures of judgment and technic.

There are two factors upon which evaluation rests. Both are of equal importance. The first of these concerns the skill with which the operative procedure is performed; that is, the skill of the surgeon and his helper, the anesthetist. It is to be assumed that the surgeon's and anesthetist's skills are of the best, but it is well to emphasize the point that it is not what is done, but who does it that may determine the outcome. All of the careful analyses of the patient's functional capacity, all of the preoperative and postoperative care amount to nothing if skill is not present. Often, too much emphasis is placed upon the immediate operation and anesthetic instead of calculating, as well as one possibly can, what the postoperative

complications are likely to be and the chances of their occurrence. The actual risk of the operative procedure itself is not very great, rarely more so than in the patient with a normal heart. It is a stormy postoperative course that wears the patient down.

The second important factor is a careful analysis of the patient's cardiac status. Statistical studies such as those recently published by Butler, Feeney and Levine¹ show us that providing we use certain sensible criteria, which draw the careful distinction between cardiac disease and cardiac failure, the risk in cardiacs is only slightly above that to be expected in persons with a normal heart.

The New York Tuberculosis and Heart Association² has published the Criteria for Classification and Diagnosis of Heart Disease. Its value is that it makes possible a plan for constructing the diagnosis in a manner that makes one arrive at a judgment. This classification takes into consideration: (1) etiology, (2) anatomical variations from normal, (3) physiological findings and (4) functional classification.

All four factors are important, for before evaluating the individual one must be able to diagnose correctly. After all, the subjective findings such as dyspnea, palpitation, etc., are not always due to organic heart disease. They are merely the signs of an embarrassed circulation which may result from a multitude of causes other than organic heart disease. One must first, therefore, ascertain the status of the patient as far as the first three items above mentioned are concerned. Then one comes to the fourth and, for our purposes, perhaps the most important.

It is the advances of recent years that have taught us to think in terms of physiological concepts. By that I mean physiological in the true sense—a science which deals with living things, *i. e.*, not how a heart appears when dead, but what are its capabilities in terms of work when alive. In cardiac disease this concept draws attention not necessarily to the disease alone, but also to failure of the heart. This important factor has been interpolated into the proper analysis as the functional classification.

FUNCTIONAL CLASSIFICATION OF PATIENT

Class I.—Patients with organic heart disease able to carry on ordinary physical activity without discomfort. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or chest pain. Patients in this class do not show physical signs of cardiac insufficiency and rarely signs of active heart infection.

Class II.—Patients with organic heart disease unable to carry on ordinary physical activity without discomfort.

II A.—Activity slightly limited. Ordinary physical activity causes undue fatigue, palpitation, dyspnea or chest pain. Patients in this class rarely show physical signs of cardiac insufficiency or signs of active heart infection.

II B.—Activity greatly limited. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or chest pain. Patients in this class usually show one or more physical signs of cardiac insufficiency or the anginal syndrome or signs of active heart infection.

Class III.—Patients with organic heart disease and with symptoms or signs of cardiac insufficiency at rest, unable to carry on any physical activity without discomfort. There is fatigue, palpitation, dyspnea or chest pain at rest. Patients in this class show marked physical signs of cardiac insufficiency or the anginal syndrome or signs of active heart infection.

This classification is not stationary but concerns the status at the time of the examination. The patient may improve and gain a place in a higher bracket. This functional classification can only be arrived at by a very careful history making which appraises the individual's subjective, as well as objective, reaction to the ordinary strain of life. The history tabulates, for example, the presence of fatigue, dyspnea, pain and palpitation, and the amount of effort necessary to bring these symptoms about. It measures their severity and whether they are growing worse or better over a period of time. The history must be so directed as to discover positive findings of vague statements. By that I mean, the number of flights of stairs, the subway steps, the elevated stairs, a hill on the farm, the number of blocks on a level street, the influence of cold wind, and of emotional stress. All these, and more, must be carefully evaluated in comparison with the normal reaction. One

must critically listen to the patient's story, for impressive and important as the stethoscope or electrocardiogram may be, they do not carry the factor of safety or reserve that is ascertained by what the patient is able to do. The findings of the so-called "functional tests" may be added to these if necessary. With a few notable exceptions, the type of cardiac lesion is not necessarily important, certainly not so much so as what the heart is able to do. As Marvin³ has said, "a damaged heart, whatever its physical signs, is the equivalent of a normal one for anesthesia and operation if it is carrying on an adequate circulation under ordinary circumstances of life."

Emergency cases cannot be evaluated for it is to be understood that they must be done and "no cardiac status per se is a contraindication to an emergency operation."

With certain exceptions, which will be mentioned later, it seems that the following general indications hold good.

Class I.—Patients that are in this group, with proper care, should be able to withstand any procedure that a normal heart would withstand. Naturally, care should be taken to safeguard against any undue strain.

Class II A.—Patients in this group should not be operated upon unless there is a definite and serious need. Although the chances for the successful outcome for the ordinary procedure are good, care should be taken to avoid any procedure which is likely to have a prolonged febrile convalescence, or stormy postoperative course. One should be particularly careful in this group, and even more careful in the group following, to weigh the ultimate prognosis against the misery and possible benefits of the surgical procedure. Of course, the latter problem must usually be solved by that omnipotent master known as judgment. It is well, however, to bear in mind an old statement, "a patient is better off half cured than all dead."

Class II B.—Patients in this group should fall into the almost emergency class. Operation should be deferred if possible until they are sufficiently improved by rest and medication to fit into one of the above brackets. Any operative procedure is contraindicated unless it is aimed to help relieve their cardiac condition or unless it is unavoidable. Their chances of operative recovery are less than those in the II A group.

Class III.—Patients in this group should not be operated

upon unless it is absolutely unavoidable, or unless it is done as a definite palliative procedure, such as total thyroidectomy.

Additional physical findings other than those needed for functional classification may influence your opinion as to the patient's capacity for surgery. But of the physical findings of the patient it should be emphasized again that it is not so much the presence of heart murmurs, or enlargement, or character of tones that are important in the physical examination, but rather the careful search of the patient for the evidence of cardiac, or impending cardiac failure. The obvious signs of failure, such as peripheral edema, enlargement of the liver, cyanosis and so forth, are too well known to require further elucidation here. Such changes must be watched for that may have a bearing on postoperative complications in the patients that do not show extreme grades of failure. For example, moisture at the bases of the lungs, this so often presages cardiac failure and often may form the favorable conditions for bronchopneumonia to start, in an area where there is diminished circulation. The liver size may be of great importance, particularly when after severe failure all other signs have improved yet the liver remains large. This usually indicates that failure may return very easily. It must be remembered that all these findings must be considered—the history, the physical examination, the fluoroscopic and the electrocardiographic examinations, and the indications given by the functional classification.

There are certain exceptions to the above generalizations and certain conditions which require emphasis.

Age has considerable influence on risk—the younger the individual the better the chances. The effects of the repeated attacks of rheumatic disease and of advancing arteriosclerosis naturally increase the severity of the pathological changes. However, age alone should not contraindicate surgery.

Extreme grades of stenosis, whether they be of the valve or of the coronary arteries, are not very likely to stand either sudden or prolonged strain. Mitral stenosis, due to rheumatic disease, is almost always accompanied by sufficient subjective and objective symptoms and signs to make one aware of the proper functional classification. However, there are occasional patients that have gradually limited their activities so that the history may be obscured. The functional test may be of

particular value in these cases. Cases of extreme aortic stenosis are also poor risks, whether the lesion is due to rheumatic disease or arteriosclerosis. There are two factors responsible, one the physical burden this type of lesion places upon the heart, and the second, that the mouths of the coronary arteries are likely to be involved with a narrowing process.

Patients with syphilitic heart disease are often unexpectedly bad risks, possibly because of the usual concomitant narrowing of the openings of the coronary arteries. In syphilitic heart disease one must also very carefully weigh the matter of prognosis against the benefit of operation. Once the syphilitic heart starts to fail it seldom, even with the best of treatment and rest, returns to its ability to maintain an adequate circulation. Even total thyroidectomy was of no benefit in decreasing the rapid downward course of the syphilitic patient that had started failure.

The greatest risk in any kind of cardiac disease comes in coronary thrombosis. In the report of Butler, Feeney and Levine,¹ the mortality in this group was 44.5 per cent, as compared with 4.9 per cent in the total group, or 2.1 per cent in the valvular group. Part of this may be due to the fact that these patients may be operated upon during an acute attack because of a mistake in diagnosis, as pointed out by Butler, Feeney and Levine. However, they should not be operated upon during an attack, or within a period of several months following if it is at all possible to avoid it.

The mortality percentage of angina pectoris is about 7 per cent. The early case of angina is not so great a risk as those cases that have had one or more attacks of coronary thrombosis. The latter develop general cardiac failure with unpleasant frequency after operation, and when this failure develops, treatment seldom benefits them.

This increased risk is likely to hold in all of the arteriosclerotic group, particularly is it true in cases showing the bundle branch block, as reported by Herrman and Herrman.⁴ This particular diagnosis shows the value of the electrocardiogram in emphasizing the status of the patient, for the lesion is seldom recognized without electrocardiographic assistance.

Cardiac arrhythmias often cause considerable concern to the patient and to the surgeon, although they are seldom serious.

The one serious one, as far as risk is concerned, is that of complete heart block of organic nature. Auricular fibrillation in itself is not a contraindication to operation, providing that it is properly controlled by the use of digitalis. Butler, Feeney and Levine¹ gave the mortality risk as being 3 per cent. Extrasystoles have no significance unless when accompanied by other findings of advanced cardiac disease. Auricular flutter also forms no contraindication by itself, but it would be preferred that it is controlled before operation. Paroxysmal tachycardia does not contraindicate operation.

Conclusion.—If a cardiac patient is selected by using the criteria mentioned, the patient's chances of surviving an operation are good. If allowance is made for modifying findings, the most simple and reliable guide is for the patient to be classified according to his functional capacity. The patient must be evaluated, not the risk.

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SPASTIC PARAPLEGIAS: THEIR DIFFERENTIAL DIAGNOSIS

THE concept that the diagnosis of an organic disease of the nervous system can be made only by those familiar with neuro-anatomy, neurophysiology and neuropathology, is unfortunately too generally accepted by the intelligent general practitioner. His tendency, when encountering such a patient, is to regard him as an unfamiliar and unwelcome guest of dubious conduct, and to show him a not-excessive cordiality. This attitude of uncertainty is reflected in his disposition of the patient. If the physician lives in a large center where neurological consultants are available, he immediately calls one in, not for confirmation of his diagnosis—a procedure which can hardly be criticized—but for the making of the diagnosis. If he lives in a smaller center or in an isolated district, he usually adopts a “laissez-faire” attitude which is readily understood when one realizes how much more important the familiar acute infection or grave injury must appear to him. It is the common experience of neurologists that many precious days and weeks are thus lost through uncertainty as to what is wrong with the patient, and the doctor's consequent failure to decide on the proper thing to do, and to do it. This short paper is written with the hope that it may help the practitioner solve some of these problems.

The diagnosis of involved organic cases undoubtedly demands the employment of knowledge gained by long intimacy with clinical neurological problems and the aid rendered by expert laboratory assistance, but the type of patient for whom this expert aid is required is fortunately less common than that type which presents a simpler neurological problem.

I fully believe that the practitioner *should and could* make a reasonably satisfactory diagnosis in most of his neurological patients who belong in the second category. He can do this if he is conversant with the general principles of neurological diagnosis, and is observant of those rather striking clinical manifestations of neurological dysfunction, the consideration of which, by a process of selection and exclusion, finally leads to a correct diagnosis. Perhaps this belief on my part can be best supported by utilizing a specific clinical problem in which the principles indicated above are followed. Let us consider, therefore, the problem of a patient who enters the physician's office with the complaint that his legs are weak, and that he cannot walk as well as formerly; or perhaps, that he cannot walk at all.

Disturbances of locomotion are met with from infancy to old age, but the scope of this paper will not permit consideration of all types. The more frequent and more important locomotor disorders (with the exception of infantile paralysis) occur during adolescence and maturity. Our discussion will be confined to a differential diagnosis of the more common types of paraplegias affecting the legs as they occur during those age periods. The refinements of neurological diagnosis will not be considered and an effort has been made to present the data in a simple and nontechnical form. In this paper only the spastic paraplegias will be differentiated, but it is hoped in a subsequent paper similarly to discuss the flaccid paraplegias and the problem of treatment.

SPASTIC PARAPLEGIAS

The spastic paraplegias present in the legs the *spastic paralytic syndrome*. This syndrome is seen on occasion in its entirety, but occurs frequently in an abortive or fragmentary form. Even though this be so, it is usually possible for the practitioner to make correctly the diagnosis of spastic paraplegia. The spastic paralysis with its associated clinical phenomena is due to a variably located lesion affecting the "upper motor neurone," that is, the corticospinal neurone (pyramidal tract) which originates in the large Betz cells of the motor cortex of one cerebral hemisphere, and whose axone crossing the midline in the medulla oblongata ends around the motor cells of the anterior horn of the cord on the opposite

side (Fig. 166). As this neurone has both an intracerebral and an intraspinal course it is obvious that either a cerebral or a spinal lesion may produce the syndrome. The clinical distinction between an upper motor neurone cerebral lesion and an upper motor neurone spinal lesion is, that in the former case the spastic paralytic syndrome is usually unilateral and on the side opposite to that of the lesion, as is seen in the ordinary cerebral h miplegia, and in the latter the syndrome

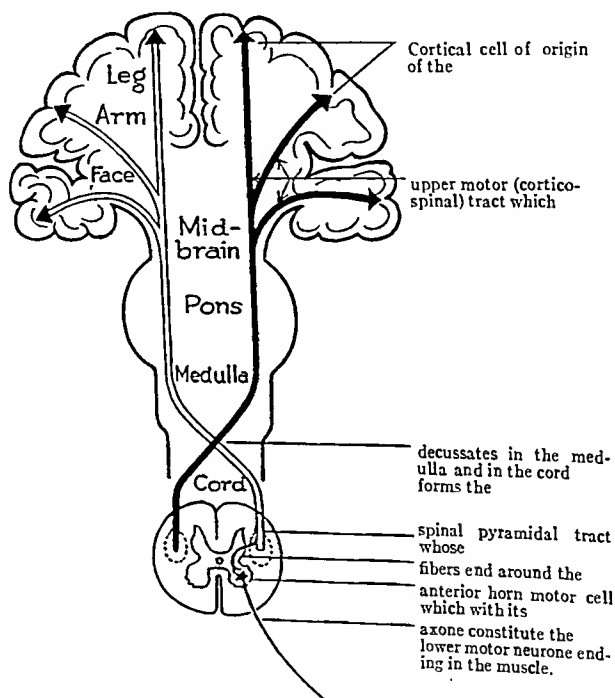


Fig 166.—Diagram showing course of the upper and lower motor neurone fibers.

is usually bilateral affecting both legs, or all four extremities if the lesion be sufficiently high (cervical cord). What are the characteristics of this spastic paralytic syndrome?

1. Increase of muscle tonus producing a varying rigidity.
2. Muscular weakness.
3. Alteration in tendon and cutaneous reflexes.
4. Absence of qualitative electrical changes in the paralyzed muscles.
5. Absence of nutritional atrophy in the paralyzed muscles.

1. **Increase of Muscle Tonus.**—The muscle tone is usually definitely increased. This is noticed on palpation of individual muscles and on passively attempting to flex or extend the various segments of the limbs. In pronounced cases, the spasticity is sometimes so marked that much force has to be employed to effect a change in the relations of the limb segments to each other, and when this force is no longer exerted, they return to their former relative positions of extension or flexion. This spasticity is often not very noticeable when the patient lies in bed, but it becomes strikingly evident when he attempts to walk. He then exhibits the spastic paraplegic gait. As his toes touch the floor, numerous tremors and jerkings of the leg are commonly observed, and a definite ankle clonus may persist until the full weight of the body is borne. The entire leg stiffens into rigid extension and as the patient walks, it is apparent that the normal flexion of the various segments of the leg is lacking. The toes and outer side of the foot tend to scrape along the ground and it is only by a great effort that he is able to raise them from the floor to which they seem to be glued, and in fact, in severe cases, are glued, for although the patient's legs support him, he cannot initiate locomotion. The whole extremity moves "as of one piece" and the tendency is for it to be carried forward by an anterior inclination of the trunk with rotation toward the opposite side. The gait is naturally slow and hesitant and any attempt to accelerate it increases the spasticity. This muscular spasm is the main element in preventing satisfactory locomotion in most of these patients. In pronounced cases, spasm of the adductor muscles may produce "scissors gait" which still further hinders progress. The definitely established spastic paraplegic gait is easily recognizable, and no one should fail to diagnose it. The early stages of its development present greater diagnostic difficulty, but here the patient often aids us by his complaint of "stiffness" on walking, and even at this early period of evolution, he shows a tendency to scrape the toes, evidenced by his shoes being peculiarly worn at the toes and outer sides. The normal spring in the gait is lost, and the patient complains that his feet stick to the ground. He walks more slowly than before, and with greater effort. His balance is less secure especially on turning. Considering the

ensemble, a careful observer can prognosticate the oncoming paraplegia.

2. Muscular Weakness.—This is present to some extent in all spastic paralyses, but the spasm so often overshadows the paralysis that its existence may escape the observer's attention. However, the muscular weakness can be demonstrated in those patients where rigidity is not too great by having the recumbent and (as far as possible) relaxed patient move the various segments of the limb against resistance. Where the limbs are fixed in abnormal positions by excessive spasm and contracture it is obvious that the existence of the paralysis can only be assumed. Usually in the flexor group the weakness is much more evident than in the extensor group of muscles, which latter, even in badly incapacitated patients may appear to possess almost normal strength. The paralysis and the spasm do not develop *pari passu*, and one who sees a number of such patients is struck by the great individual variation in the paralysis where the spasticity appears approximately equal in degree.

3. Alteration in Reflexes.—(a) *Tendon Reflexes.*—There is a striking increase in the patellar jerk, suprapatellar jerk and the ankle jerk. This is present on both sides, but not necessarily equally so. The reflex is usually greater on the side more affected. The extension of the leg on the thigh as the patellar tendon is struck is extremely brusque, the amplitude of the movement is great, and the violent muscular contractions so induced often overflow into associated muscle groups, sometimes even to those of the opposite leg. Temporary, and later, permanent ankle clonus are usually demonstrable. It should be noted that these reflexes increase proportionately with the spasticity up to a certain point, but the spasticity may be so extreme that the tendon reflexes cannot be elicited. This is especially the case when the contracture is of the more unusual flexor type.

(b) *Cutaneous Reflexes.*—If the paraplegia be of any degree of severity, the cutaneous reflexes are similarly profoundly altered. The normal flexion of the great toe induced by the stroking of the outer portion of the sole of the foot is usually replaced by the extension of this toe (Babinski reflex). This, if clear cut, indicates without reservation an upper

motor neurone (pyramidal tract) lesion. It is of diagnostic, but not necessarily prognostic import, as it may later disappear, and perhaps again reappear. As the lesion producing the spastic paraplegia is usually a cord lesion, alteration of the cutaneous abdominal reflexes whose centers are in the lower dorsal cord segments, is often noted. These reflexes are usually decreased or abolished, occasionally normal, rarely indeed exaggerated. They are ordinarily more decreased or abolished on the side more affected (compare with tendon reflexes). In all testing of reflexes it is essential to compare those of one side with those of the other side, and also if possible, to compare the abnormal with the normal.

4. **Electrical Reactions in the Spastic Muscles.**—It is well known that electrical reactions in paralyzed muscles are of both quantitative and qualitative nature. The qualitative changes occur in lower motor neurone lesions and include the reaction of degeneration, partial or complete, and this will be described briefly in the discussion of flaccid paraplegias. In lesions of the upper motor (corticospinal) neurone this reaction of degeneration is not met with, at least not in its complete form. The electrical changes in upper motor neurone lesions are merely quantitative, *i. e.*, increased or decreased excitability of the muscle to the faradic, galvanic, or the combined galvano-faradic currents. These changes when they occur are of no particular diagnostic or prognostic significance. The testing of the muscle reactions to the electrical current in spastic paralysis is not therefore a part of the routine diagnostic procedure. It is done only under exceptional circumstances, as for instance, when a marked and localized muscular atrophy is present in, or adjacent to, the spastic extremity. Discussion of these reactions in spastic paralyzes need not therefore be further considered.

5. **Muscular Atrophy.**—As the affected corticospinal neurone ends around the anterior horn cells of the spinal cord, it has no direct connection with the paralyzed muscles. Muscular atrophy in such muscles is seldom pronounced. Atrophy that is evident is principally due to disuse of the muscles, and this atrophy of disuse may vary considerably depending upon many factors. It is sometimes very noticeable, but is seldom extreme. The usually excellent nutritive condition

and lack of atrophy of the entire paralytic musculature is in striking contrast to the nutritional disturbances so evident in the flaccid paraplegias. In some patients where the muscles are strongly hypertonic, one might assume from clinical observation that a mild condition of muscular hypertrophy actually exists.

The practitioner having definitely classified his paraplegic syndrome as of the spastic or the flaccid variety is now faced with the problem of etiological diagnosis. This can be made in many instances after a careful consideration of the complaints of the patient, the chronological development of the symptomatology, and the existing physical signs. These last can be usually elicited by a physician who does not possess a special technic, but who is acquainted with the simpler methods of neurological examination. The solution of the typical case should be the objective of the practitioner, and this objective he can usually attain. In order that confusion may be avoided, only the entities most commonly presenting the spastic paraplegic syndrome as it is met with in a general neurological hospital, or in general practice will be discussed.

The following diseased conditions which produce the spastic paraplegic syndrome will be considered in the sequence indicated:

1. Multiple sclerosis.
2. Spinal cord tumor.
3. Syphilis of the spinal cord.
4. Combined sclerosis of cord with pernicious anemia.
5. Myelitis.
6. Trauma.
7. Spastic paraplegias with lower cervical cord syndrome.
8. Tuberculous spinal caries.
9. Malignant growths of the spine.

MULTIPLE SCLEROSIS

This diagnosis is frequently made by the neurologist, and the tendency is to make it either by associating a characteristic and suggestive history with certain frequently found signs and symptoms, or by excluding other entities, which may produce a similar paraplegic syndrome. In the latter case the neurol-

ogist makes the tentative diagnosis of multiple sclerosis, which presumed diagnosis may embarrass him six months or a year later, when the appearance of additional signs indicates the correct diagnosis. However, even by this process of exclusion the diagnosis is usually correct, and is therefore justifiable.

The classical tetrad of signs—nystagmus, intention tremor of arms, scanning speech and optic atrophy—is very seldom observed in its entirety. Even in a large neurological hospital where many spastic paraplegias are seen, months frequently elapse before a patient with the textbook picture of multiple sclerosis presents himself. Considerable individual variation in the symptomatology is bound to occur, owing to the entirely unsystematic way in which the plaques of sclerosis are scattered throughout the entire cerebrospinal axis, but by and large, any spastic paralysis in which there is a cerebral symptomatology is suspect as to this diagnosis. Most stress must be laid upon the concurrence of one, or preferably more, of the aforementioned signs, with the history of the striking remissions so often described by the patient. In addition although this is not represented in the accompanying table, before making a final diagnosis much consideration must be given to the absence of characteristic signs and symptoms met with in other conditions producing spastic paraplegias. As an example of this, the absence of spinal block of the cord neoplasm, of the positive serology of the luetic, of the achlorhydria and blood picture of the combined sclerosis may be cited. This weighing of the positive factors and the negative factors applies to all diagnoses, and the more meticulously it is done, and the more the results are thoughtfully considered, the less will be our percentage of error. By this dual appraisal, it is safe to say that the physician will find himself in error in his diagnosis of only an exceptional patient.

The cerebrospinal fluid is negative except for the rather frequent occurrence of a gold curve suggestive of paresis. In cases where doubt exists the presence of this curve—syphilis being excluded—may be a determining factor in establishing the diagnosis.

SPINAL CORD TUMOR

A tumor within the spinal canal obviously may be outside the dura, or within it. If within, it may be in the interior of

the cord (intramedullary) or lying upon its external surface (extramedullary). It may exist at any vertical level between the uppermost cervical and the lowest sacral segment. The tumor in its relation to the surface of the cord may lie on its anterior, lateral or posterior aspect. In consistency it may be hard and encapsulated, or soft and infiltrating. All these, and other unmentioned factors, produce variations in the symptomatology. These variations cannot be discussed here, as we are attempting only to diagnose differentially the spastic paraplegic syndrome of which cord tumor is one producing cause. The reader may refer to any one of the numerous excellent textbooks on neurology for further details as to cord tumor symptomatology. It may not be amiss, however, to remark that as most tumors are situated posteriorly in the vicinity of the sensory roots, the early picture in the majority of patients is that of shooting "root" pains in the trunk or limbs, and later, loss of sensation in the painful areas, followed ultimately by the syndrome of cord compression. When the tumor lies anteriorly and the motor roots are pressed upon, we have muscular atrophy (hands and arms in cervical lesions, thighs and legs in lumbar lesions) followed ultimately by the syndrome of cord compression. Lastly, when the tumor is on the lateral aspect of the cord, spastic paraplegia exists on the same side, below the level of the tumor; on the opposite side, also below the level of the tumor, there is loss of pain and temperature sensibility (Brown-Séquard syndrome), followed ultimately by the syndrome of cord compression.

As a matter of fact, the diagnosis of spinal cord tumor is hardly that of tumor, but rather that of *increasing* cord compression, which compression syndrome manifests itself clinically in two ways, first by a progressive sensory paralysis (anesthesia below level of lesion) and second by a progressive motor paralysis (spastic paraplegic syndrome). Among neurological patients cord tumor is the most frequent etiological factor in producing this progressive pressure symptom. We assume, therefore, that unless there are definite reasons to think otherwise, a tumor exists when the clinical syndrome of cord compression is present.

All evidences of pressure are not clinical. Compression is also indicated by important chemical changes in the cerebro-

spinal fluid, as indicated in the chart, and by the interruption of the free circulation of this fluid (spinal block). Such block is determined by the Queckenstedt manometric test.¹

These changes indicating compression similarly do not necessarily point to tumor, although they usually do. However, tumor can exist without a block. A considerable percentage of small tumors, or tumors located within the cord, do not show a block. This important fact must not be overlooked. The level of the tumor is usually determined by the level of the objective sensory loss, but it is not always possible to definitely determine this.²

To summarize, we may say that if we can eliminate trauma and caries by the history, the physical examination and the x-ray procedures, we can assume a tumor as being the most likely cause of the clinical and spinal fluid changes indicating compression.

The diagnosis between a tumor and multiple sclerosis may be made with approximate certainty in the majority of cases. On the one hand the presence of a sensory level with evidence of spinal block, and on the other the occurrence of characteristic remissions and intracranial symptoms, with no sensory level, enable us to make, without too great hesitancy, the differential diagnosis between multiple sclerosis and cord tumor.

¹ *Queckenstedt Manometric Test.*—The cerebrospinal fluid within the intracranial cavity, and that within the subarachnoid space of the spinal canal, constitute one freely circulating and communicating fluid system. An increase in intracranial pressure brought about by compression of the jugular veins with resultant distention of the intracranial veins, is therefore immediately transmitted to the spinal canal, and this increase is indicated by a rise in the fluid in the manometer, which is attached to the lumbar puncture needle. The jugular pressure being released, the fluid pressure returns to normal. Both rise and fall occur within a few seconds. If the needle be inserted below a tumor entirely blocking the spinal subarachnoid space, there can be no fluctuations in pressure when the jugulars are compressed or released. If the tumor does not entirely fill the space, the rise and fall occur but over a longer period of time. Normal pressure of the fluid is about 150 to 200 mm. of water.

² *Lipiodol Test.*—When a block exists, and we cannot determine its level by clinical investigation, we may be aided by an injection of lipiodol. The lipiodol is injected in the first cervical interspace, and descends the length of the spinal canal. The point of its arrest as determined by the x-ray is approximately the tumor level. It is obvious that this test is only to be made by those experienced in the technic.

SYPHILIS OF THE SPINAL CORD

Syphilis of the spinal cord rarely exists alone. The brain is usually involved, and the condition is really one of cerebro-spinal syphilis, although the symptomatology may not indicate brain involvement.

As all structures constituting the cord may be affected by the varying pathology, it is easily understood that the clinical picture may also vary greatly. Unclassifiable types occur, but we distinguish grossly three main clinical groups. These are as follows:

1. Progressive spastic paraplegia of almost pure type, with minimal subjective and objective sensory disturbances. The paraplegia develops very slowly, the onset occurring usually some years after the date of the initial infection. The pathology is principally confined to the pyramidal tracts.

2. Progressive spastic paraplegia associated with or preceded by "root" pains over a period of weeks or months, indefinite sensory loss in these painful areas, and perhaps spinal rigidity and tenderness (chronic syphilitic meningitis). This type of spinal lues is perhaps that most commonly met with. It ordinarily develops earlier and progresses more rapidly than the purely spastic type. The sensory disturbances are due to involvement of the meninges, with consequent root irritation. The resemblance of this form to spinal tumor is sometimes striking.

3. Progressive spastic paraplegia developing weeks or months subsequent to an acute flaccid paraplegia (acute transverse syphilitic myelitis). Here we have the initial picture, and subsequent course of an ordinary acute myelitis (*q. v.*), and we must differentiate it from other forms of myelitis. The syndrome is usually due to thrombus formation in diseased arteries, with resultant immediate paralysis, and subsequent cord softening (myelomalacia). We see therefore that spastic paraplegia is common to all forms of spinal lues, differing in individual patients in the time of its development, in its associated symptoms, and usually in its intensity.

The diagnosis of spinal syphilis is based upon:

1. A history of specific infection. Unfortunately this is often lacking in patients with syphilitic involvement of the nervous system, as are the usual secondary symptoms.

2. Existence of signs indicating intracranial involvement. The most important of these is of course pupillary disturbance, especially failure of the pupil to react only to accommodation, or only to a light stimulus (Argyll Robertson pupil), or to both.

3. Blood or spinal fluid findings indicating the existence of lues. One cannot rule out syphilis of the nervous system merely because the blood Wassermann is negative. This is often the case, and in exceptional instances, even the spinal fluid may be negative also. However, it is rare to see untreated lues which does

not give either a positive blood Wassermann or a positive spinal fluid Wassermann if in testing 1 or 2 cc. of fluid is used. The colloidal gold test shows a "luetic curve." Some color is lost from a variable number of the ten tubes, but it is rare to have all color discharged in certain tubes, as is the case in paresis. The spinal fluid shows an increase in the cell count from a score to several hundred. Both protein and globulin are usually present in greater than normal quantities. In many old, nonactive cases especially if they have been thoroughly treated all findings may be normal.

For purposes of this paper, we may regard a patient who gives neither history nor signs of past specific infection, whose pupil outline and reactions are normal, and whose serology is negative in all respects, as a paraplegic of nonsyphilitic origin. An error will seldom result if these criteria are applied.

COMBINED SCLEROSIS OF CORD WITH PERNICIOUS ANEMIA

The term "combined sclerosis" is a descriptive pathological term, and is applied to any condition in which two or more of the great longitudinal systems of motor or sensory fiber tracts of the cord are undergoing degeneration and sclerosis. Such a combined sclerosis is often found in infections, intoxications, and deficiency diseases affecting the central nervous system. When a neurologist uses this term, he almost invariably refers to the combined sclerosis associated with pernicious anemia, a sclerosis affecting principally the pyramidal tracts (upper motor neurone) and the posterior sensory columns of the cord, (Fig. 167). These columns conduct impulses of deep sensibility (vibratory and joint position sense) to the cerebrum. We observe, therefore, as may be expected, two orders of symptoms, first a motor symptomatology (spastic paraplegia) occurring as a result of the pyramidal tract lesion, and, second, a decrease or loss of perception of vibration and lack of recognition of the position of the distal joints, these occurring as a result of the posterior column lesion. Such motor and sensory losses do not always develop in a definite order or necessarily at an equal rate. However, as a general rule the exaggeration of reflexes usually precedes the objective sensory loss, although subjective paresthesias in the hands and lower limbs are often complained of at the earliest stage of the disease. Rarely indeed do we have a definite sensory level as is the case with tumor, and never spinal block. The blood

picture in the vast majority of patients is that of a severe or mild pernicious anemia. This with the almost universally associated achlorhydria gives us an ensemble of signs and symptoms which makes the diagnosis obvious. In addition the absence of cerebral signs and symptoms is important for diagnosis, as they are rarely met with. Diagnosis should be made early and all patients with pernicious anemia who com-

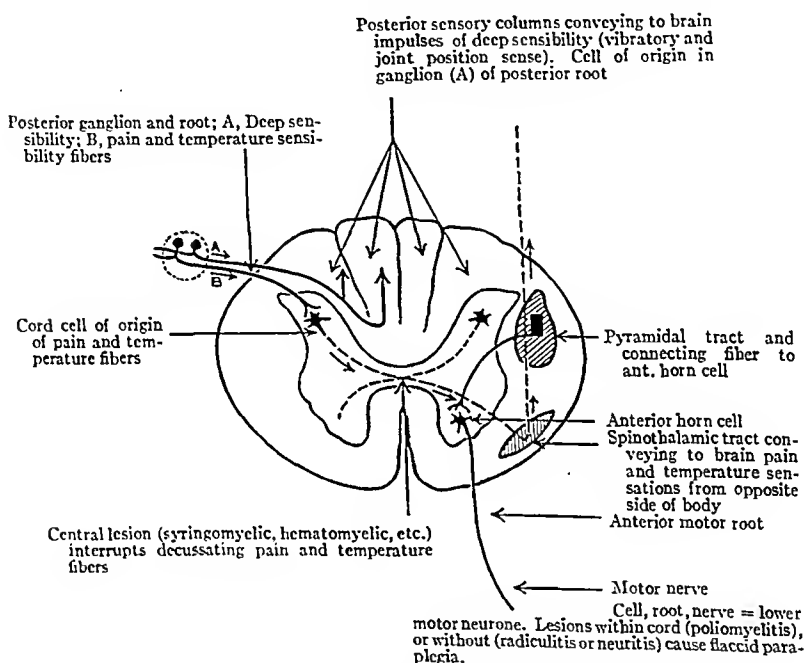


Fig. 167.—Schematic cross section of the cord showing course of fibers of pain and temperature sensibility, deep sensibility, and the pyramidal, spinothalamic, and posterior column tracts.

plain of numbness or tingling of the extremities, or of a similar paresthetic belt surrounding the trunk, should undergo a rigid neurological examination, to determine whether the early stage of a spastic paraplegic syndrome with accompanying disturbance of deep sensibility exists. If so, intensive and appropriate treatment must be at once instituted if advancing cord degeneration is to be halted.

SPASTIC PARAPLEGIAS WITH LOWER CERVICAL CORD SYNDROME

The lowest (eighth) cervical segment and the first thoracic segment of the cord are of especial interest to the neurologist in connection with the spastic paraplegic syndrome. In the anterior horns of these two segments lie the cells whose nerve fibers, leaving by the anterior roots, supply the intrinsic muscles of the hands, the interossei, the lumbricales, and the muscles of the thenar and hypothenar eminences. In these segments exists also a center for the sympathetic dilating mechanism of the pupil of the eye. The neurones from this center similarly leave the cord by the anterior roots of the eighth cervical and first thoracic segments and run up through the cervical sympathetic cord in the neck to end ultimately in the dilating fibers of the pupil. Therefore, it can be readily understood why a destructive lesion involving these cord segments, or the motor roots coming from them, produces paralysis and atrophy of the small muscles of the hand (with degenerative fibrillary twitching of the muscles), and a miosis of the pupil due to the unopposed action of the pupil constricting fibers. The miosis is usually associated with a slight ptosis and enophthalmus (Horner's syndrome). The association of these two orders of symptoms (the muscular paralysis and atrophy being the more constant and more important) constitutes a localizing syndrome for this portion of the spinal cord. When this syndrome is associated with spastic symptoms in the legs, the neurologist usually thinks, first, of amyotrophic lateral sclerosis (the spasticity being due to a concomitant pyramidal tract degeneration) or, second, of syringomyelia (the spasticity being produced by pressure of a central glial mass [or a cavity] which involves the pyramidal tract). The absence of objective sensory loss in amyotrophic lateral sclerosis and its presence in syringomyelia, definitely determines the diagnosis. In syringomyelia tactile perception is little affected, but pain and temperature perception is either diminished or lost (syringomyelic dissociation).¹ Other dis-

¹ It must not be forgotten that this muscle atrophy-pupil contraction syndrome indicates only a specific anatomical lesion of these segments. A spinal cord tumor, a localized syphilitic meningitis or a localized trauma, etc., affecting this region, may produce the same symptomatology. The diagnosis of these conditions has been elsewhere considered.

We may envisage the syringomyelic dissociation in the same way. It is

tinguishing differential points between amyotrophic lateral sclerosis, syringomyelia and other conditions will be found in the accompanying table.

TUBERCULOUS SPINAL CARIES

Spinal caries is one of the most frequent causes of spastic paraplegia. Caries occurs most frequently in children and young adults. The caries is practically always secondary to a tuberculous process existing elsewhere in the body, and the demonstration of such a lesion allows one tentatively to presuppose the diagnosis of Pott's disease. The characteristic angular "gibbus" deformity of spinal caries is usually present in the later stages. As is well known, deformity may exist without paraplegia, but the paraplegia may also exist without deformity. As a rule pressure producing the paraplegia is due rather to a cold abscess or a pachymeningitis, than to pressure by diseased or displaced bone. The thoracic spine is most frequently affected.

The first symptom is usually referred to the spinal column, and consists of localized pain in the diseased vertebrae or of pain in regions supplied by the sensory roots entering the spinal column in proximity to the diseased vertebrae. The pain is increased on weight bearing, and on twisting or jarring the spine, and is lessened by the recumbent position, or, more completely, by immobility. The pain is often worse at night as the protective muscular spasm which, during the day, tends to immobilize the spine, disappears during sleep. As a result of this muscle spasm, the second most important symptom, that of spinal rigidity, develops, demonstrated by the usual methods of testing spinal mobility. Tenderness on pressure or percussion over the diseased spines may be evident, but is frequently absent as the early lesion is usually in the anterior portions of the bodies of the vertebrae, far removed from the vertebral spines.

not specific for syringomyelia. It is merely an anatomical syndrome due to the fact that the fibers conveying heat and temperature sensations pass through the cord in the vicinity of the central glial tumor or cavity, and are thus interrupted (Fig. 167). Central hemorrhage (hematomyelia) which may be due to trauma, myelitis or vascular disease, or centrally located cord tumor, will produce this same dissociation.

Neurologically the picture is clinically, and often from the point of view of the cerebrospinal fluid, that of gradually increasing cord pressure as previously described under cord tumor. It is probably true that the pressure symptoms develop more rapidly than they do in tumor, and it is certainly

Reflexes

Any reflex (cutaneous or tendon) disappears if its center is destroyed. Generally speaking a lesion of the cord increases the tendon reflexes below that level and decreases the cutaneous, with the production of a Babinski.

Muscle tone

Slowly developing cord paralyses are usually spastic except in lumbosacral lesions (flaccid). Suddenly developing paralysis is first flaccid, later spastic except in lumbosacral lesions which remain flaccid.

Sensation

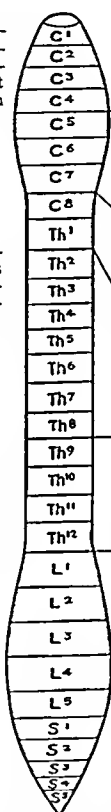
Superficial—Touch, pain, temperature.

Deep—Vibratory (tuning fork) and knowledge of position of joints. Sensory loss in adequate lesions usually involves the body from the level of the lesion down. For the skin areas supplied by the various segments and roots see any segmental sensory chart.

Lower motor neurone

See Figs. 166 and 167

Lesions of this neurone produce a flaccid paraplegia syndrome, viz.:
Reduced muscle tone
Decreased or absent reflexes.
Muscular atrophy.
Reaction of degeneration.



Cervical 1-4
Pain in neck muscles and back of head.
Neck held stiffly or abnormally.
Sometimes weakness and atrophy of posterior neck muscles.

Cervical 5-7
Pain in shoulder muscles, upper arm, and outer side of arm.
Atrophy and paralysis of biceps, deltoid and sometimes triceps.
Biceps, triceps and radius reflexes lost.

Cervical 8, Thoracic 1
Pain along inner side of arm.
Atrophy and paralysis of forearm finger flexors and intrinsic hand muscles.
Horner's ocular syndrome
Radius reflex lost.

Thoracic 2-8
Intercostal neuralgias.
Paralysis of intercostal muscles (difficult to demonstrate).

Thoracic 9-12
Pain in abdomen and hips (operation for nonexisting abdominal diseases common).
Paralysis of abdominal muscles.
Upper and lower abdominal reflexes lost.

Lumbar 1-3
Pain lower back and thighs.
Atrophy and paralysis of psoas, adductors, and extensor thigh muscles.
Knee jerk and cremasteric reflexes lost.
Sphincter and genital disorders marked
Paralysis usually flaccid

Lumbar 4 to Sacral 5
Pain lower back, in senile distribution and perineum.
Atrophy and paralysis of flexors of thigh and muscles below knee
Absence of ankle jerk and plantar reflexes (no Babinski)
Sphincter and genital troubles extreme
Paralysis flaccid

Fig. 168.—Cord segments with symptomatology. The above symptomatology schematically represented is only relative but should aid considerably in diagnosis of level.

true that the distressing "root" pains and objective sensory disturbances are less severe in these patients. An obvious reason for the lack of severe root pain is the integrity until late in the disease of the intervertebral foramina through which the roots emerge. The motor signs and symptoms are always more pronounced than the sensory. The sensory signs are always improving.

ment, even to apparent cure, that may occur in a severely paralyzed patient is very dramatic, and is met with in no other type of cord paralysis. Occasionally the signs of compression manifest themselves rapidly because of the sudden collapse of eroded vertebrae. As a rule the familial and personal history, a possible temperature rise in the evening, the early spinal pain and rigidity, the discovery of other tuberculous lesions, the local deformity and tenderness, and the usually conclusive x-ray findings, enable the physician to make the diagnosis without reservation. Marked objective sensory disturbance and marked flexion paraplegia are distinctly unfavorable features as regards ultimate recovery.

MALIGNANT GROWTHS OF THE SPINE

In considering the etiological diagnosis of spastic paraplegias, the possibility of malignancy must not be overlooked. Sarcoma, which may be either primary or secondary in the vertebrae, and carcinoma, which is always secondary, are the most frequently encountered malignant tumors. In any case of suspected cord tumor, the thyroid, breast, lung, gastrointestinal tract, uterus and prostate should be carefully examined for primary malignant new growth. Metastatic implantations to the vertebral column usually occur late in the course of malignant disease.

Among the most characteristic symptoms are the extraordinarily constant and distressing pains of a root type running around the trunk and down the limbs, the distribution being determined by the level of the segment affected. These pains, while of a general root character and distribution, are remarkable in usually showing no clear-cut objective sensory loss in the skin areas supplied by the affected roots. They are at first intermittent and mild, later constant and excruciating. The contrast between the fugitive and comparatively mild pains of caries, and the agonizing pains met with in malignancy, is very striking. It is to be noted that in caries extension of the spine shortly relieves the pain, but it does not in malignancy. These pains and the muscular atrophies often noted in the painful extremities are undoubtedly due to the very common involvement of the intervertebral foramina, through which pass the anterior and posterior spinal roots.

Local spinal pain and tenderness are not at all infrequent. Deformity may exist; if so, it is usually rounded and not angular as in caries. Do not confuse this with the tumor masses of sarcoma which may sometimes be palpated in the vicinity of the spinal column.

The course is usually rapid, and the symptoms frequently develop in a certain order, namely, first, bone symptoms, second, root symptoms, and, if the patient lives long enough, the phenomena of cord compression. It is rare for the spastic paraplegic syndrome to be as marked as in other conditions previously discussed. Constitutional symptoms, such as a progressively increasing cachexia and anemia, and a continuous loss of weight lend support to the diagnosis of malignancy. If the primary focus cannot be discovered, the diagnosis may remain debatable until cancerous erosion of the vertebrae is revealed by the x-ray. We should not, however, hesitate too long in accepting the diagnosis of malignancy, as this definite roentgenographic proof may be lacking for weeks, or even months, and the patient may thus be deprived of treatment which, by relieving his pain, might at least make his unhappy lot more endurable.

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DIAGNOSTIC TABLE OF SPASTIC PARAPLEGIAS

Anamnesis and history	Multiple sclerosis		Spinal cord tumor.	Syphilis of cord (cerebrospinal syphilis).
	Usually 25 to 35.	Progress over years. Frequent remissions, sometimes approximate return to normal.	Any age, especially third, fourth and fifth decades.	Usually middle adult life.
Principal complaints.	Stiffness and weakness of legs. Tremor of hands. Vision decreased. Speech impaired. May complain that eyes "jerk." Vague sensation of heat, cold, numbness, "pins and needles" in extremities. Dizziness.	Stiffness and weakness of legs. "root" pains around trunk, down legs. Sneezing, coughing, increase pains. Sometimes local pain in vertebral near tumor site. Variable genital and sphincter disturbance.	Onset gradual. Progress over months or years. No definite remissions.	Often no history of primary infection. Course as for tumor. (Exception myelitic form.)
Clinical findings.				
Brain.	Yes (speech, tremor, etc.).	None.	None.	Rare.
Cranial nerves.	Vision decreased. Central or paracentral scotomata. Pallor of optic discs. Nystagmus especially on lateral gaze. (Slight pupil changes or paralysis of extra-ocular muscles.)	No involvement.		Sometimes involved, especially pupil reactions and extra-ocular muscles (paralysis), diplopia.
Motor signs.	Syndrome of spastic paraplegia; (same syndrome often in arms). Intention tremor of arms (finger-nose test).	Syndrome of spastic paraplegia. (Exception: in lumbosacral growths mixed or flaccid paraplegic syndrome.)		Syndrome of spastic paraplegia (for variations see text).
Sensory signs.	Rarely a demonstrable patchy loss of touch, pain, and temperature perception. Vibratory and joint position sense more affected. A sensory level uncommon.	Early increase, later decrease of sensation in painful root areas. Demonstrable loss of superficial and deep sensibility below level of cord lesion. "Sensory level" exists. (See note, Fig. 168.)		Often no demonstrable change. If present never as pronounced or clearly limited as in tumor (except in myelitic form).
Other findings.	Sphincter and genital disturbances rare except in advanced cases. Speech tends to be "syllabic," "explosive," emitted with difficulty.	Atrophy and paralysis (for distribution see Fig. 168). Root pains in cervical and lumbar cord (see Fig. 168).		Possibly local chancre scar or other signs of past luetic infection.
Laboratory.				
Spinal fluid.	Usually normal. In a large percent the gold curve is haretic or luetic (condition is not luetic). Fluid Wassermann negative.	"Spinal block" exists (see text). Protein increased (Normal 25 to 40 mg.). Globulin present (Normal 0). Fluid yellow or clots. Cells about normal (0 to 8).		Wassermann positive 50 to 80 per cent depending on type of infection. Globulin and protein increase. Fluid usually clear. Cells increased score to humbrelts.
Other reports.	Blood Wassermann negative.		Blood positive in 50 to 80 per cent.
x-Ray.	No related findings.	Lipiodol may indicate tumor level (see text).		No related findings.

	Combined sclerosis (with pernicious anemia).	Acute myelitis.	Trauma of cord.	Lower cervical cord syndrome.	Tuberculous spinal caries.	Vertebral malignancy.
Age.	Usually middle adult life.	Any age.	Any age but more common in adult life.	<i>Syringomyelia</i> 15 to 30. <i>Amyotrophic lateral sclerosis</i> 35 to 50.	Children and young adults.	Adult life.
Course and history.	Slowly progressive, seldom remissions if untreated. Remissions possible if consistently treated.	<i>Rapid onset</i> within a few hours to a day or two. <i>Variable recovery</i> over weeks or months.	<i>Rapid onset</i> , minutes to hours. Recovery as for myelitis. <i>History of injury</i> usually obtainable.	<i>Syrin.</i> Variable rate of progress. Frequent arrests. Duration years to lifetime. <i>A. L. S.</i> <i>Lethal exit</i> 1 to 5 years.	Slow progression to paraplegia. <i>Retropulsion and arrest at any time.</i> Relapse not uncommon.	<i>Rapid progress.</i> No remissions. No arrests. Symptoms develop usually: 1. Bone, 2. Roots, 3. Cord.
Principal complaints.	Paresthesias, belt form or in hands and feet. Aching, indefinite pain of these parts. Clumsy hands. Stiffness and weakness of legs.	Paresthesias and numbness around trunk and down limbs. (Seldom severe pain.) Partial or complete paralysis below level of lesion. Variable genital and sphincter disturbance.	Pain at site of injury. Other symptoms very similar to those of myelitis.	In <i>both diseases</i> : Weakness, wasting of hand muscles. Stiffness and weakness of legs. <i>Syrin.</i> Burns, pricks, cuts himself without pain. <i>A. L. S.</i> Progressive inability to articulate and swallow.	<i>Vertebral pain, worse on weight bearing, jarring, moving spine.</i> (Immobility, extension reduce pain.) <i>Stiffness of spine.</i> Stiffness and weakness of legs. Radiating "root" pains not very common.	Pain in spinal column. <i>Agonizing "root" pains.</i> Stiffness and weakness in legs.
Clinical findings.						
Brain.	None.	None.	None unless concomitant brain injury.	None.	None unless intracranial complications.	None unless brain metastases.
Cranial nerves.	None.	In certain rare forms optic neuritis with optic disc congestion.	None unless concomitant brain injury.	<i>Syrin.</i> Paralysis and atrophy of tongue not rare. Sometimes sensory loss fifth nerve. <i>A. L. S.</i> Paralysis of vocal cords, palate, pharynx, tongue, lips common. Atrophy and fibrillations of the muscles.	None unless intracranial complications.	None unless brain metastases.

Symptoms of spastic paraplegia		As for acute myelitis.		Syndrome of spastic paraplegia follows the primary flaccid paraplegia		Syndrome of spastic paraplegia.		Syndrome of spastic paraplegia not pronounced and only if the patient lives long enough.	
Other findings.	Indefinite peripheral loss to touch, pain and temperature. Vibratory and joint position sense decreased or lost especially in feet.	Sensory loss varies below level of lesion from complete, affecting all types, to partial, affecting only certain types of sensation. "Sensory level" common.	As for acute myelitis. "Syringomyelic dissociation" (see Fig. 167) if central hemorrhage (hematomyelia); syndrome at times suggested.	Syrin. and A. L. S. Symp. Atrophy and fibrillations of paralyzed muscles especially arms and in A. L. S. Increased reflexes in arms in A. L. S.	Demonstrable sensory loss rare (severe cases only).	Objective sensory loss not common and definite sensory level rare.	If spinal deformity usually round projection. Malignancy elsewhere.	Normal or syndrome of partial block. Complete block not common.	Demonstration of malignancy in other tissues, fluids, etc.
	Constitutional signs and symptom of pernicious anemia (glossitis, lemon color to skin, etc.).	Fever occasionally. Systemic or local infection may exist. (Often virus unknown.)	Signs of local trauma. No fever unless wound, or vesical, or decubitus infection.	Syrin. Kyphoscoliosis. Often vasomotor disturbances. In both diseases: Horner's syndrome at times (v. text).	Angular deformity, "gibbus." Tuberculosis elsewhere. Early spinal stiffness. Evening temperature rise?				
Laboratory.	Normal.	Fluid clear. Variable increase in cells and protein; or fluid normal.	Fluid clear to bloody. Cells, protein, etc. vary widely. Sometimes cord compression picture with "block."	In both normal.	Normal, or may have syndrome of partial or complete block.		Demonstration of tuberculosis germs in fluids, tissues, etc. elsewhere.	Demonstration of malignancy in other tissues, fluids, etc.	Malignant erosion of vertebrae, ribs or other skeletal structures.
	Blood picture of pernicious anemia more or less clear (usually precedes cord symptoms). Achylarhydria 90 to 95 per cent.	Blood picture may suggest existing infectious process.	Definite evidence in vast majority of patients of vertebral injury.	Syrin. Vertebral deformities. A. L. S. No related findings.	Thinning of intervertebral discs. Erosion of adjacent vertebral margins. Later extensive destruction of body.				
Other reports.	No related findings.	No related findings.	Definite evidence in vast majority of patients of vertebral injury.	Syrin. Vertebral deformities. A. L. S. No related findings.	Thinning of intervertebral discs. Erosion of adjacent vertebral margins. Later extensive destruction of body.		Demonstration of malignancy in other tissues, fluids, etc.	Demonstration of malignancy in other tissues, fluids, etc.	Malignant erosion of vertebrae, ribs or other skeletal structures.
X-Ray.	No related findings.	No related findings.	Definite evidence in vast majority of patients of vertebral injury.	Syrin. Vertebral deformities. A. L. S. No related findings.	Thinning of intervertebral discs. Erosion of adjacent vertebral margins. Later extensive destruction of body.				

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THE MALE SEX HORMONE

History.—Since antiquity, man has attempted male sex gland therapy. In 1678, Leeuwenhoek described a substance recovered from the testes as "spermin." In 1776, Theophile Bordeu compared the characteristics of the castrate capon to the eunuch, and attributed to the testes the function of sex development, and sex characteristics. Seventy-three years later Berthold demonstrated that the results of castration in the rooster, followed by caponizing effects, were soon overcome by reimplantation of testicular tissue. Since the rooster's comb, barbles, wattles, and feathers are excellent test tissues for the demonstration of potent testicular tissue, we utilize these in testing and standardizing potent preparations.

In 1850, Franz Leydig described the interstitial cells of Leydig. "They contain lipoid granules in their cytoplasm," and also cholestrin, esters, and fatty acids, and are found in groups, as polyhedral epithelial-like cells. "They bear some resemblance to some cells of the suprarenal cortex. In the four-month-old embryo, when sex differentiation becomes apparent, they occur in large numbers. At birth they are fewer in number. At puberty they are abundant, and diminish in number during the male 'climacterium.' They occur between the seminiferous tubules, arranged around the blood vessels and lymphatics." They are stimulated by the gonadotropic hormone of the anterior pituitary gland.

In 1889, Brown-Séquard dramatically announced his own rejuvenation, using extracts made from dog and guinea-pig testes. His enthusiasm was shared by few. If anything, it helped to retard the progress of the subject. In 1903, Bouin and Ancel showed that ligation of the vas deferens in animals

halted spermatogenesis, but that the interstitial cells proliferated. Later it was observed that in bilateral cryptorchids, spermatogenesis is absent, the interstitial cells may be present, secondary sex characteristics may be normal, libido and potentiality little affected, and the phallus normal. Thus, little by little the chain of evidence attributed to the testes two separate functions, the external "spermatogenic," and internal "hormonic" (linked to the cells of Leydig). Biedl, in 1916, emphasized well known medical knowledge that disease of the epididymis and atrophy of the seminiferous tubules do not influence sex impulses or secondary sex characteristics, nor produce retrogressive changes in the organs or their function.

In 1908, Walker, and in 1911, Pezard produced comb growth in capons by injections of testes extracts, followed in five months by crowing and sexual behavior. By 1927, McGee had so concentrated the material, demonstrating that the lipid fraction of bull testes was richest in active hormone, that only five days' injections or assay was necessary. Then, extracts of calf, swine, and stallion testes, were found to yield biologically proved extracts, potent in about five days' administration.

Anatomy and Histology.—The testes arise from celomic epithelium, proliferate, and form the germinal epithelium. Mesoblast, underlying, thickens and forms the genital ridge, with an interlocking of epithelial and mesoblastic cell masses. From the epithelial cells develop the seminiferous tubules; from the mesoblasts, the stroma and vascular tissue. Included in this stroma are epithelial cells—the interstitial cells.

The descent and extrabodily location of the testes are no mere accident. If testes are subjected to intrabodily temperature for some hours, spermatogenesis ceases. Their external position, therefore, maintains a temperature at which the function of spermatozoa formation progresses.

Within the tubules spermatogenesis takes place. Proliferation of the spermatogenic cells is stimulated by the pituitary gonadotropic hormone. "Other smaller columnar-shaped cells are found lying among the spermatogonia, with their bases, which are somewhat conical in shape, resting upon the basement membrane. These cells are the cells of Sertoli." (Their possible functions and secretion of inhibin are purposely avoided to simplify this discussion.)

It is the present conception that the comb-stimulating factor is made in the cells of Leydig, but not stored. It is a constant moving process with waves and recessions of function, the pure hormone being carried off into the blood, producing its action, broken up and being eliminated in various forms, some detected in the urine, but having much feebler comb-stimulating and other similar powers.

Effects of Excision of the Gonads.—Removal of the gonads prevents mature sexual development, secondary sex characteristics failing to make their appearance. "Castration of male frogs prevents the appearance of the sexual changes which normally occur during the mating season. The sexual development of birds and mammals is profoundly affected by castration. The castrated leghorn cockerel (capon), has a greater proportion of body fat than the normal bird, while the comb, wattles and barbles, and the sex instincts do not develop. Castration of young bulls causes an increase in size of the skeleton and a greater deposition of fat. The mature development of the accessory organs is prevented. Castration of boys before puberty retards ossification of the epiphyses of the long bones, with consequent enlargement of the stature. The lower limbs become disproportionately long. There is also adiposity, the fat tending to become feminine in distribution. The larynx is not prominent as in the mature male, and the voice remains high-pitched. The hair fails to grow upon the face and body, but is plentiful on the head. The penis remains infantile, sexual feeling is suppressed" (Best and Taylor).

In animals, castration results can be nullified, more or less, by sufficiently large secreting testes grafts. Ovariectomized females can be made to assume male characteristics by successful grafts. The degree of response of an individual character depends upon the quantity of hormone present—or the amount, number, etc., of the grafts.

Following gonadectomy, the pituitary gonadotropic hormones are found in the blood and urine in greatly increased amounts; the pituitary gland enlarges; the basophils of the pituitary increase in number and many become enlarged, distended with some clear fluid substance, the nucleus pushed to one side—producing the so-called "signet-ring" or "castration

cells." Reimplantation of gonadal tissue, or injection of potent extracts, reverses the pituitary picture to the normal. Removal of the gonads (male or female) permits increased and unrestrained output of pituitary gonadotropic hormones, giving rise to excessive amounts in blood and urine. This also occurs in the menopause (male and female). Potent testicular implants or extract injections decrease this output, while increasing amounts will further depress the output of the pituitary gonadotropic hormones.

The Unit of Male Sex Hormone.—The standardization of the potent extract was gradually improved. It would stimulate capon comb growth, and later was shown to restore the state of the accessory sex organs (penis, seminal vesicles, prostate, etc.). Ancel and Bouin, in 1900, following injections of glycerol extracts, observed the changes in the seminal vesicles and penis of castrate guinea-pigs. Various other methods of observing effects of potent extracts and standardization were suggested, such as: (1) A spermatozoon motility test; (2) amounts required to produce certain weight changes in the prostate of castrated rats; (3) seminal vesicle reactions; (4) seminal vesicle weight test; (5) restoration of bill pigmentation of the castrated English sparrow; and so on. However, Gallagher and Koch suggested that the unit be described as the "amount which injected per day, for five days, yields an average of 5 mm. increase in length and height of the combs on at least 5 brown leghorn capons."

With the demonstration of the presence of various hormones in the urine, extraction of male urine for male sex hormone was begun. At first the yield was small, but as improvement followed improvement, it appears that some general averages in yield can be described, although daily outputs fluctuate widely. The yield from fresh testis tissue, still low, is about 1 unit per 50 to 150 Gm.

In 1931, Butenandt obtained a pure crystalline male hormone from human urine. Its formula was $C_{16}H_{26}O_2$, but later another androsterone was found with the formula $C_{19}H_{30}O_2$. A second urinary male hormone fraction was then separated, dehydro-iso-androsterone. Meanwhile McGee, and Gallagher and Koch had obtained a substance from testis tissue approximately ten times as potent as the urine derivative. Then.

Laquer, *et al.*, 1935, obtained from the testis extracts crystals of exceptional potency, with the formula $C_{19}H_{28}O_2$, termed testosterone. Since then, Ruzicka and also Butenandt have been able to synthesize pure testosterone in the laboratory, from cholesterol, together with 31 (or more) other androgenic substances, some of which have already been found in urines in various pathological conditions. Their order of activity is not the same on capons and rats, nor the same for seminal vesicle and prostate reactions.

It was readily shown that synthetic male sex hormone would replace the effects of castration, if its use was not postponed too long; its action on the accessory sex organs being stimulation of growth and function of Cowper's gland, the penis, the preputial tissue, periurethral tissue, etc. Some of the androgens had a theelol- and theelin-like action on female animals, as well as simulating progesterone, and stimulating the mammary glands. They will hasten the involution of the thymus, prevent suprarenal enlargement and changes following castration, and affect the pituitary, its function and histology, as has already been referred to.

There has been no demonstrated specific action on muscle tone or efficiency. It has not been shown to have the suspected oxidative catalytic action. It does not hasten metabolic processes or raise the metabolic rate. Androgenic substances are also found in female urine, and elsewhere. Conversely, male urine, testis, etc., have been shown to contain estrogenic substances (female sex hormone). In the urine of normal males and females, certain ratios exist between androgenic and estrogenic substances and various pathological states are associated with deviations from these ratios (as in homosexuality, virilism, masculinization, effeminization, hypertrichosis, etc.).

Use in Humans.—Some observers have used testosterone in humans. Its effect in a postpubertal castrate was described recently by G. L. Foss, while Hamilton has made several observations on human eunuchoidism. Others have likewise reported a few results. Some of our own results are the following:

Cases I and II.—N. M. and B. B. are classical examples of "Frölich's syndrome," with infantile genitalia. They are aged thirteen and fourteen respectively, and have failed to respond to the usual therapy, which included

diet, exercise, thyroid and pituitary and pituitary-like gonadotropic hormone injections. Since their parents repeatedly called our attention to the lack of genital growth, we gave each testosterone propionate¹ intramuscularly—25 mg. testosterone propionate every second or third day, for about three weeks, with the following observations: Within about six to ten days repeated erections began to occur, the scrotal tissue became reddened and thickened, and the scrotal sac seemed to enlarge; the penis began to enlarge, became redder, and took on a more normal appearance. On ceasing the injections, the tissues seemed to shrink, and tended to return to their former state, but the recession was not to the former level. Thus, the penis remained fully one fifth to one third larger, the scrotum remained larger, and some more pubic hairs appeared. It was observed by everyone, that their former shyness, and effeminate characteristics were distinctly decreased, and replaced by more "boyish" or "manly" carriage, talk, walk, and attitude.

Case III.—R. R. is twenty-four years old. At the age of ten years, because of bilateral cryptorchidism, operative attempt was made to bring both testes down into the scrotum. The wounds sloughed, and the operation failed in its intent. In less than a year, a second such attempt was made. Since, he has grown to his present height (74½ inches), with typical eunuchoidal characteristics, measurements, female configuration, infantile genitalia, no facial hair, scant suprapubic hair, and complete lack of sexual feeling or desire. Treatment over a period of two years with gonadotropic hormones produced some change—slight growth of suprapubic hair, slight genital enlargement, etc. However, introduction of treatment with testosterone propionate was followed by most striking results: 18 daily injections of 10 mg., 4 injections of 25 mg. in two weeks, and 3 injections of 50 mg., 1 every third day, all within about six weeks (a total of 435 mg.). There followed penile enlargement (about 100 per cent), numerous frequent erections, leading to onanism and orgasms with emission of a clear albuminous liquid. Even more striking was the change in the mental attitude and spirit.

Case IV.—M. F., aged twenty-nine. This is a more complex case. At twenty-six years of age, he came to the clinic with these chief complaints: (1) enlarged breasts; (2) female configuration; (3) small genitalia; (4) lack of libido, erections, etc. His urine contained fairly large amounts of estrogenic substance, but exceedingly small amounts of androgenic substances. Very slight changes followed pituitary-like gonadotropic hormone administration. Plastic operation on his breasts brought some mental and physical relief. In one month, recently, he received 525 mg. testosterone propionate with the following results: (1) marked increase in size of penis; (2) marked increase in size of scrotum; (3) increase in frequency, number and intensity of erections; (4) onanism now yields orgasm and copious amounts of a clear albuminous liquid.

Case V.—H. W. came under observation at the age of twenty-one years. He was a typical hypopituitarism, height 63 inches, with no facial and few

¹ The testosterone propionate (oreton) used was supplied by Schering Corporation, Bloomfield, New Jersey, through the kindness of Dr. Max Gilbert.

suprapubic hairs, infantile genitalia, and a history of complete lack of sexual desire or ability. For about twelve months, he received pituitary growth hormone and gonadotropic hormone. He grew $2\frac{1}{2}$ inches in height, and his genitalia showed slight improvement, with moderate growth of suprapubic hair. Then he received 14 injections of testosterone propionate totaling 350 mg. over a period of seven weeks. The results were striking! Erections, at times bordering on priapism, appeared. Sexual desire and libido became very marked. The genital tissues seemed to become edematous, and almost doubled in size. Marked reddening of the penis, scrotum and surrounding skin appeared. Omission of injections was followed by some recession. More striking still was the change in his carriage and mental attitude. Resumption of treatment is again producing similar results.

Case VI.—O. R. is twenty-eight years old. He is a more marked hypogonadal individual, probably of pituitary origin. He came under observation about four years ago. The penis measured about 1 inch, erections never occurred, no testes could be palpated, the scrotum was proportionately small. There were no facial hairs, and only a few suprapubic hairs. Treatment for three years with pituitary gonadotropic hormone produced some, but very slight changes. Recently he received 15 injections of testosterone propionate (totaling 400 mg.) in about five weeks. The results are less striking than in other cases, but definite genital enlargement has occurred. The number of erections are increasing and libido has appeared.

Cases VII, VIII, IX.—We chose 3 cases of adult impotency for study. One we believed received inadequate treatment (6 injections totaling 60 mg.) and the result was negligible. The second case was a male, aged fifty-five, who has had impotency and loss of libido for five years. He received 5 injections of 25 mg. testosterone propionate (1 every second day) and then 4 injections of 50 mg. each (in twelve days), totaling 325 mg. The results were most striking. The third case has just begun treatment.

We have deliberately avoided the discussion of the theory of the production of benign hypertrophy of the prostate, and the possibility of treatment with male sex hormone. However, in the cases of impotency just cited, they had had 3 to 6 nocturnal urinations for four to five years, but as treatment continued, these became less in number, so that at the end, nocturia occurred but once a night (and was omitted on many occasions).

Impression of Results of Treatment.—All who have attempted to treat cases, such as I have cited, know of the almost hopelessness and helplessness of all forms of therapy hitherto tried. The pituitary or pituitary-like gonadotropic hormones held forth some hope of improvement, but with little actual improvement or result. However, soon after administration of this substance in sufficient amounts, something began to take place, more in some cases than in others—in one or

two, very striking. Stimulation of libido, male sex instinct, erections, growth of tissue and organ, enlargement of the scrotal sac, some growth of hair, all these were more or less definite. Even more striking was the change in the mental attitude, cheerfulness, hopefulness, and spirit. They became more alert and despondency vanished.

On a number of occasions, placebos, injections of plain oil, or 2 to 5 mg. doses of testosterone propionate (oreton) were substituted. This check has been likewise carried out by other observers, and all agree that it is not a "psychic" or "mental" result, but "real," and to a certain extent, effects and result depend on dosage, which still requires standardization. The dangers of overdosage or long continuance are still real and present. We have not demonstrated spermatogenesis, but have obtained emissions of fluid (probably of prostatic and seminal vesicle origin). This requires further and longer study in selected suitable cases. The possibilities in treatment of other types of diseases have been intimated, and many questions remain for the clinician and endocrinologist to answer.

In conclusion, the synthetic preparation is definitely "active"; there was definite response in regard to stimulation of the male sexual functions including libido and potency; there was definite growth of the accessory organs; there were many agreeable psychic, psychological and mental effects. It is probably a pure replacement therapy, while time and trial will determine the side or ill effects, if any.

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**NONSURGICAL TREATMENT OF ACUTE AND CHRONIC
SINUS DISEASE WITH OPERATIVE INDICATIONS
AND CONTRAINDICATIONS**

Nomenclature.—Various classifications of sinus disease are given in the standard textbooks, both here and abroad, and many eminent rhinologists, through their teachings and contributions to the literature, have adopted modifications, so that a uniform system of names is still lacking.

In order to simplify the assignment given to us, it is proposed to use the very general terms "acute sinus disease" and "chronic sinus disease," and to eliminate the arbitrary term "subacute sinus disease," which latter condition it is fully realized exists in many instances.

The terms "acute" and "chronic" have reference to the element of time. The sinus condition is said to be acute when it is several hours old, lasting some ten days to two weeks. The pathology of inflammation is variable as to time, depending upon the virulence of the invading organisms, the resistance of the host, and the additional complex factors associated with inflammation and infection. Thus an acute sinus condition may clear up in a few hours, with restitution, or may carry on for many days. In uncomplicated cases, the inflamed tissue gradually returns to the normal. Where inflammation persists after two or three weeks, it may be said to have

passed the acute phase and entered either the subacute or chronic stage. When an acute sinus condition ends, and a subacute or chronic state begins, no one can, with certainty, tell clinically.

In the acute and chronic cases, mixed pathologic processes are the rule. Thus catarrhal and suppurative phenomena are so often observed together in the same case, that these terms are implied in the diagnosis, though often not used. They are seen in both acute and chronic conditions.

Intranasal evidence of structural damage, as well as compensatory tissue changes, are observed more often in the chronic cases, the etiology thereof due to pathogenic bacteria, their toxins or allergens of infinite variety, or perhaps all of these.

The terminology of acute sinus disease will take in, therefore, the catarrhal and suppurative forms, as well as allergic types, and the same nomenclature will be adopted for the chronic sinus disease cases.

It would be beyond the scope of this presentation to enter into the details of the therapy of each individual sinus; indeed the basic principles might be lost sight of, if this were undertaken. Assuming that all of the sinuses are involved, the processes being either acute or chronic, as mentioned before, emphasis will be placed upon the commoner varieties encountered in general practice.

General Considerations.—Treatment to be effective, in any given case, presupposes a correct diagnosis. This means a careful history of the local condition, its etiology, onset, complications, course, previous treatment, duration, intermittency, acute exacerbations, nose and throat history, previous operations, general health and previous attacks of illness; home, personal, and school hygiene, swimming habits, diet, etc. Following this the upper respiratory tract is inspected to note the condition of the intranasal structures, the presence or absence of exudate, the tracing of pus or mucopus to its source by means of capillary negative pressure, if possible; the presence or absence of hypertrophies or hyperplasias of the structures of the lateral nasal wall, septal irregularities, polypi, adhesions, synechiae, atrophy and ulceration, *ad infinitum*. The pharynx and fauces should be examined with care. If

tonsils are present their cryptic contents should be evacuated by expression and critically evaluated. If a tonsil operation has been performed the fossae should be examined for stumps, tags, regrowths, small crypts concealed behind the pillars or beneath scar tissue. The postpharyngeal wall should be checked for secretions and for isolated lymphatic masses, and any compensatory hypertrophies of the lateral pharyngeal folds searched. It is of the utmost importance to have a good light in order to make these examinations accurate and precise. Further aid in evaluating the finer details will be found in skillful sounding of the intranasal structures, lavage, syphonage, postnasal mirror, nasopharyngoscope, transillumination, x-ray studies with or without radiopaque solutions, and recheck of the case. A good history and a painstaking examination will, in the great majority of cases, clinch the diagnosis. Frequently x-ray studies are necessary to delineate certain details but need not be resorted to in the routine.

In view of the fact that many cases of sinus disease are caused and perpetuated by dysfunction in one or more systems of the body, it is often important that a thorough general physical examination by a competent internist be made, including blood studies, tests for syphilis, tuberculosis, sugar tolerance, anemias, cardiorenal function, endocrine system, blood pressure, and kindred functional tests.

In connection with the plea for a thorough general examination we should bear in mind what E. R. Lewis has postulated: "Purulent discharge from a sinus may be the expression of a general systemic, metabolic or nutritional wrong, of local tissue reaction to a foreign body, toxin or trauma, any of which may reduce local resistance sufficiently to give foothold to bacteria for otherwise impossible invasion of the tissues; with removal of the chief etiology, the tendency is toward spontaneous restoration of the individual to normal. In a similar manner mucosal tissue reaction to allergens or vitamin deficiency may secondarily give focal footholds to indigenous infections."

In concluding our studies, we have now arrived at the diagnosis of what type of sinus disease we are dealing with, in any given case, and what faults in the body economy may or may not be present. The nonsurgical treatment will therefore

consist of the application of such general and local measures as the history indicates.

General Measures in the Nonsurgical Treatment of Acute and Chronic Sinus Disease.—Every method should be utilized to heighten the powers of immunity, both local and general. Every system in the economy should be properly rested and exercised, and every proved hygienic principle carried out, to insure proper balance. Where dysfunction of any system or systems has been found, thorough management to restore normal function should be instituted, without delay, else the vicious circle may continue.

Care in the selection of a well-balanced diet will aid in no small way in increasing the general well-being of the patient. Fresh vegetables and greens, cod liver oil or its equivalent, milk, cream, butter, fruits, all in proper balance will supply the necessary vitamins A, B and D, and where indicated, if the case discloses nutritional faults and vitamin and mineral deficiency, additional concentrates of these important elements are available. Exercises, active and passive, attention to posture and breathing exercises, as well as massage, heliotherapy and hydrotherapy will likewise enhance physical vigor. Adequate sleep, regular periods of rest and relaxation, will materially aid the kinetic system (brain, thyroid gland, adrenal gland, liver and muscles) so that it will sustain the energy of the body as well as create a high reserve of "electric potential" (Crile). Proper clothing and the avoidance of chill and drafts help to preserve the balance of the circulatory and glandular systems, thereby preventing a lowered point of resistance to occur in the body. Mental hygiene, too, by cultivating poise and calmness, promotes functional vigor and combats physical depression. It is the judicious combination of all of these measures that will undoubtedly raise the resistance of the body to the highest possible level, aiding the elimination of recurrent acute or chronic sinus disease, if the latter condition be due to faults of personal hygiene, improper diet, fatigue, mental and nerve strain. The above outline cannot be stressed too strongly, for it constitutes definite principles and grounded fundamentals in any scheme of building up the vital powers. The adjustment of metabolic faults, the promotion of elimination, and the normalizing of faulty blood chemistry is of vital

import in achieving the best results. The endocrine system should be supported and balanced. The elimination of endogenous and exogenous poisons will be of help, in many cases.

Nasal allergy is met with in a fairly large proportion of acute and chronic sinus cases. In fact allergic disease and true sinus suppuration may coexist, the former, by obstructing ventilation and drainage, inducing the latter. Where the appropriate studies have shown allergy to exist, desensitization or avoidance of the offending allergens is the obvious course to be pursued.

Climatotherapy may be tried, where possible. Though favorable results have been reported in many cases, change of climate has not always proved to be helpful. The physician should therefore use discretion in advising patients, making it clear that the change may or may not benefit them, although in many instances it is beneficial.

Foci of infection in the throat, teeth, and other systems may perpetuate, if not cause, the sinus disease. Dean, in his studies, has shown that tonsil and adenoid infection in children bears a definite relationship to sinusitis, and a good clean-up of these infected structures has time and again proved the truth of his dictum. Constitutional diseases, specific or non-specific, any hereditary weakness, or indeed any dysfunction, should be diligently attended to, so that the sinus disease, if any relationship at all exists, may be ameliorated.

Local Measures in the Nonsurgical Treatment of Acute and Chronic Sinus Disease.—These are designed for the purpose of promoting aeration and drainage of the nose and the paranasal sinuses. They relieve pain, in most instances, and give the patient comfort. The function of the upper airway is aided, promoted and preserved, and by their use at no time is there any loss of tissue or disturbance of anatomic relations.

It is important to recall that the proper management of an acute case consists not only of curing it in the shortest possible time, but of conducting studies to see if it is indeed an acute entity, or if it is an acute exacerbation of a chronic, though latent, process, and if the former, to institute measures to prevent the development of chronicity. The treatment of chronic pathology present, whether it is general or localized in one or

more cells, how many sinuses are involved, the degree of mucosal and bony changes, the amount and character of the exudate, and whether previous surgery has been employed.

It is obvious that the acute cases are more simple to treat than the chronic, and that it may often be necessary to change from one type of treatment to another.

Local Treatment in the Acute Sinus Cases.—During the very acute stage, where the mucosa is highly engorged, very little should be done intranasally. A spray of weak cocaine and ephedrine solution and a bake before an infra-red lamp for about twenty minutes, the patient's face being kept at a distance of about 20 inches from the burner, after which a soothing oil is nebulized in the nasal chambers, is effective. Cotton packs soaked with weak shrinking solution, applied over and under the middle turbinate, can be substituted for the spray, or be used after an initial spraying, of the aforementioned shrinking agents.

Where much secretion appears in the nasal chambers, it is helpful to lavage the fossae with warm normal saline solution, and then apply cotton pledgets soaked with one of the colloidal silver preparations, allowing these to remain in the middle and superior meati for one or more hours. They can then be removed in the office or, if placed in the fossae with a strong black silk thread looped around them, or with a tail-like end made by twisting the end of the cotton and tucking it in the nose, the patient will be able to remove the medicated cotton himself several hours later, and will not have to come back to the office to have it removed. R. H. Skillern strongly advocated the use of cotton pledgets soaked in a 25 per cent solution of colloidal silver in water and glycerin, equal parts, introduced preferably hot, kept high in the meati, and for from two to six hours. Samuel R. Skillern has recently improved upon this technic by incorporating in the mass of the pack a small metal tape to which is attached the positive pole of the diathermy machine, the negative electrode being placed upon the back of the patient's neck. This generates heat in the parts being treated and seems to be very effective in some cases, but it must be used with caution, the current kept low and the time of the treatment limited to from five to twenty minutes with the current set at 250 milliamperes. It is well to start with

the minimum dosage, and if the patient experiences no discomfort, or as he develops tolerance, the current can be increased to a maximum of 700 milliamperes. Straight medical diathermy also has its advocates.

The use of capillary suction is safe at all times, but the suction cannula should be gently insinuated around the middle turbinate and the concavities of the lateral nasal wall, higher up in the fossae, and wherever secretions are noted. Mass suction, albeit valuable, should always be employed with caution. Apart from the fact that it can cause harm by inducing sudden changes of pressure and prolonging mucosal turgescence, it may damage the structures otherwise and in many ways. Nevertheless, skilful use of capillary and mass suction is valuable in the office treatment of sinus disease. Lavage, already mentioned, is likewise useful, but it should be remembered that this procedure must be performed gently, the head well down, the concentration of the salt isotonic, and comfortably hot.

These measures are the fundamental ones in the acute cases. Where the mucosal inflammation has begun to show a subsidence, and secretions are noted in the middle and superior meati, and in the postnasal space, then it might be well to use the displacement-irrigation method of A. W. Proetz. This consists in placing the patient's head with the chin facing the ceiling so that the chin and the external auditory canal are in a vertical plane, the latter of course dependent. This places the eustachian tube mouths higher up, and above the ethmoidal basin. From 2 to 4 cc. of 0.25 per cent ephedrine sulfate in normal saline solution are dropped in each nasal fossa alternately, the mass suction tip applied to the fossa just instilled, the patient remaining in the aforementioned position and uttering the sound "K-K-K," while gentle mass suction is applied intermittently not exceeding 5 inches of negative pressure on the gauge. The efficacy, according to Proetz, of this method, depends upon the dilution and liquefaction of the sinus secretions and the keeping of the medicament in contact with the inflamed sinus mucosa for considerable periods of time. The method is reasonably safe, though some middle ear inflammation has been observed in 2 cases, which may or may not have been a coincidence.

The allergic cases should be treated along the lines advocated above, in order to facilitate drainage, open up the airway and allow adequate ventilation. This will lessen the tendency to sinus involvement, although it will not cure the allergy. The latter condition must be dealt with by one thoroughly trained in the field of allergy.

Where the mucosa still fails to become decongested on application of shrinking agents, and after the subsidence of the acute inflammation, one or more chemical caustics may be used. Pure phenol, trichloroacetic acid, chromic acid, or silver nitrate, 90 per cent, can be cautiously applied to the hypertrophic or hyperplastic tissue. This cauterizes the tissue. A needle can likewise be inserted into the tissue down to the bone, and the high frequency current turned on. This is electrocauterization or coagulation. These methods call for skill and experience and should not be undertaken unless one is fully familiar with them.

Local Treatment in the Chronic Cases.—The method here follows the general principles used in the acute cases. The use of shrinking solutions, packs, lavage, colloidal silver medicaments, capillary or mass suction, infra-red irradiation, displacement-irrigation, syphonage, cauterization, topical applications, or postural drainage, skilfully performed will aid the physiological efficiency of the nose and its accessory sinuses. At no time should pus or mucopus be permitted to accumulate in any of the cells or sinuses. Exudate not draining freely interferes with the normal mechanisms of the intrasinus and intranasal structures. Where ventilation and drainage are free, these mechanisms have full play to function as nature intended them to function. The cilia, blanket of mucus, blood vessels, phagocytic cells and other elements function at their best when drainage is free and the aeration abundant.

It is not amiss to repeat that the conservation and preservation of the functional mechanisms of the nose and accessory sinuses will depend directly upon the attainment of "good ventilation and free, uninterrupted, continuous drainage," so strongly advocated by Herbert Tilley, of London. When the local and general measures are combined in the manner indicated above, favorable results should be the rule.

Oral and Parenteral Medication in the Office Procedures.—Bicarbonate of soda and various forms of iodine drops have been used empirically by physicians for a good many years, and the results were often sufficiently gratifying to merit the continuation of these substances. Numerous explanations for the improvement noted have appeared from time to time in the literature, though up to the present time no final opinion has been declared. The general trend, however, inclines to the view that alkali reserve factors, so often depleted in the acute upper respiratory infections, are maintained at the proper level when bicarbonate of soda is given, and that iodine promotes the general metabolism.

It has been felt that oral and parenteral medicaments, given judiciously, might well supplement, in appropriate cases, our tested local procedures. Some of the acute and chronic sinus cases will improve by the adjuvant therapy of 3 units of insulin, hypodermically, and the oral administration of 3 minims of an official or proprietary compound iodine solution with $\frac{1}{2}$ teaspoonful of bicarbonate of soda in a full glass of water, following a treatment, preferably on an empty stomach. The iodine-soda dose may be repeated three times daily and the insulin once daily as suggested by D. C. Jarvis.

The most gratifying results of this form of treatment will be found in the very early cases of acute head cold which are potential sinus infections and which, in general, respond very well to the insulin and iodine drink. It has been observed in the hospital wards that many sluggish wounds will heal much quicker when small doses of insulin are administered. The explanation for this is highly conjectural, but it is not unlikely that cellular nutrition is improved by virtue of better assimilation, better oxidation and better elimination of waste. Many authorities are of the opinion that small doses of insulin improve the general nutritional state of the body by promoting the better assimilation of food stuffs, or helping the cellular elements to improve their own nutrition. Other drugs that may be administered parenterally that will often give gratifying results are camphor, menthol and iodoform in peanut oil, put up in sterile ampules. Such preparations are on the market. The most striking results are obtained in the acute cases, and in the acute exacerbations of low-grade chronic

sinus infections, though some chronic cases exhibiting minor grades of endocrine imbalance were benefited. This combination of drugs is given daily in some cases following local treatment, or, when prolonged treatment is necessary, semiweekly or weekly. The pharmacodynamic value of these preparations is apparent when one studies the properties of the drugs contained therein. Where insulin and iodine give no results, this preparation in some instances has seemed to help considerably. It is emphasized that this is no cure-all, but that the mode of action of this preparation differs considerably in its physiologic effects from insulin.

Many patients report that, since suffering one or more acute attacks of sinusitis, or acute exacerbations of chronic sinus disease, they are more prone to fatigue and physical exhaustion than before the incidence of the infection. These types often show intranasal evidence of a mucosa that is relaxed and atonic, with a feeble response to vasoconstricting agents, even though hypertrophy or hyperplasia is entirely absent. For such cases marked improvement may be noted by giving them hypodermically, in addition to the regular office treatment, an ampule containing the cortical substance of the adrenal gland with traces of the medullary substance put up in such a manner as to obtain a more prolonged action of this important hormone. Thus the titer of this preparation is slightly higher in the blood for a period so that the adrenal gland is not put to further strain in order to supply the bodily need for this substance. This enables the adrenal gland to rest.

Good stock vaccines are of value in many cases. The initial dose should be small, gradually working up to the maximum, at intervals of seven days, for a period of from 10 to 20 injections, in accordance with the teachings of J. A. Kolmer. It is customary to start with 0.1 cc. of "catarrhal vaccine" and increase the dose by 0.1 cc. every week, to the maximum of 1.25 to 1.5 cc. Autogenous vaccines are possibly more valuable but care must be taken in obtaining the culture. This must be done by a rhinologist and the vaccine prepared by an expert. It should be remembered that an improperly prepared autogenous vaccine is of much less value than a commercial stock preparation. Good results have been reported

following the administration of nonspecific protein therapy, such as milk or its commercial substitutes, but it has failed us in the chronic cases. The value of the local application of vaccine is questionable, and the more modern bacteriophage is too new to be properly evaluated.

Measures to Be Carried Out by the Patient at Home.—

It is an acknowledged fact that our homes are overheated and very dry during the winter months. If the ventilation were improved and the humidity raised the nasal mucosa might possibly benefit thereby.

It is customary to advise steam inhalations to all of our acute sinus cases, regardless of the etiology. One teaspoonful of the compound tincture of benzoin to a pint of steaming water, to which a few grains of menthol have been added, makes an efficient vaporization. This the patient inhales deeply not more than ten minutes at any one time, several times daily, for comfort. He is not permitted to go outside. The medicated steam is very soothing and actually decongests the inflamed mucosa. As an alternative a general continuous vaporization of the entire room is useful as a means of increasing the humidity. Windows should not be widely opened at night. The more closely the night room temperature approaches that of the daytime, the less strain there will be on the ciliated mucous membrane of the nasal passages. Above all else, drafts must be avoided.

Drops of weak ephedrine sulfate (0.25–0.5 per cent) in normal saline solution or 0.25 per cent neosynephrin hydrochloride are instilled in each nostril, with the head well back, this position to be kept for two minutes. This should be performed several times a day. Sprays of the same solution may be used, very gently, repeated in about five minutes. The first spray will decongest the lower turbinates, so that the second spray will penetrate further and reach the deeper and higher structures. Mild constriction of the nasal mucosa is produced by these methods, ventilation and drainage is promoted, and the patient rendered more comfortable. Ephedrine in oil in the form of drops or spray is often useful for adults and older children, but should not be used in the case of infants, because of the possibility of inducing lipopneumonia. Solutions containing cocaine should never be prescribed for home use. Col-

loidal silver preparations, administered in the form of drops, have some popularity. If used in chronic cases these drops should not be used for too long periods for fear argyria may develop.

Drug Therapy.—Judicious use of drugs will help to bring about further balance in many cases. Where stimulation is needed, in vitamin deficiency, mild grade of subthyroid imbalance, autonomic imbalance, mineral deficiency, general lack of tone, poor appetite and lack of digestive and assimilative vigor, faulty elimination, subnormal oxidative metabolism, and in many more kindred conditions, so often associated with acute and chronic sinus disease, drug therapy may exert a favorable influence.

Strychnine sulfate, very small daily doses of thyroid extract, calcium therapy, belladonna, phenobarbital, dilute hydrochloric acid, brewer's yeast, cod liver oil concentrates, specially prepared perles containing the necessary vitamin units, mixed vitamin with iron, liver-stomach concentrates, vitamin B complex, ephedrine sulfate, will in many instances prove useful adjuncts to treatment, so that the patient using these regularly when indicated will benefit because of the improved condition of the bodily constituents and greater functional capacity.

Sulfanilamide, given judiciously in properly selected cases, has been very helpful. The physician should be on guard for any untoward toxic symptoms, however, during its administration.

Since rest is one of the essentials in the treatment of acute sinus disease the patient should be put to bed in the early stages and a sedative administered, if necessary, to induce sleep. Opium in any form is useful and has the additional advantage of allaying the pain from which these patients often, although not always, suffer. If mere sedation is required, any of the barbituric derivatives may be used with satisfaction. Where the pain is mild, acetylsalicylic acid in 5- to 10-grain doses usually gives relief, but if the headache is intense morphine or codein should be used without hesitation. An ice-cap over the painful area is usually acceptable, but at other times heat is preferred. In any event the patient suffering from an acute sinus infection must remain in bed until the febrile

period is passed, and in the house for some time thereafter. If there is no fever, office treatment is allowable, and indeed preferable, because of greater facility for the various local treatments described above. When the acute sinus condition is accompanied, as it frequently is, by pharyngitis, tonsillitis, laryngitis or tracheobronchitis, these complications should receive early recognition and appropriate treatment.

Operative Indications and Contraindications.—When the conservative measures mentioned above have been thoroughly tried out with failure to effect a cure, the question of surgery should be considered. Septal deviations and deformities, polypi, hypertrophies and hyperplasias of portions of the middle turbinates that block sinus ostia, should be corrected with the view of obtaining improved aeration and drainage. To use nonsurgical treatment only in the presence of a badly deviated septum or other obstructions to the airway and free drainage is to deprive the patient of the most important principle conducive to good sinus health.

Sinus surgery may be divided into conservative and radical. Conservative surgery consists in operative procedures designed to restore the individual sinus involved to normal function, with the least amount of destruction possible, while radical surgery aims to either obliterate a functioning sinus, remove a large part of its bony wall and its lining membrane, or to approach the sinus from the external route, removing infected cells, lining membrane, devitalized bone, necrosis, sequestered bone, rarefying areas, etc.

Where the intranasal mechanism has been adequately balanced and still no cure effected, then the question for further surgery must be considered.

The indications for surgery may be divided into absolute and relative, as taught by R. H. Skillern. Absolute indications may be present in either the acute or chronic cases, though in the acute cases, the most conservative treatment possible, including surgical, is the best and safest. The diagnosis or even the suspicion of an oncoming intracranial extension during the course of either an acute or chronic sinus infection, ruling out the middle ear or other cause, constitutes an absolute indication for radical operation. The symptoms and clinical signs of brain abscess, meningitis, osteomyelitis, dentigerous cysts in-

vading the maxillary sinus, the presence of a mucocele, orbital cellulitis that has not yielded to conservative treatment in the early stages but has gone on to pus formation, necrosis of the walls of the frontal, ethmoid or maxillary sinuses as demonstrated by fistula formation, tumors contained in any of the sinuses, whether they be malignant or benign, cavernous sinus thrombosis if associated with accessory sinus disease, all constitute absolute indications for radical sinus surgery of some type.

Relative indications are those signs and symptoms that may not be sufficiently severe at first to warrant subjecting the patient to a capital operation, but which may become absolute at any time owing to the development of other symptoms or increase in severity of those present. Of all cases presenting relative indications for radical operation, conservative treatment has been tried without avail, perhaps for long periods of time, until the patient finds that the continuance of the disability caused by the disease warrants or demands more radical treatment. Furthermore, what may be an unimportant symptom to an individual in one walk of life may constitute in another adequate reason for advanced surgical work for its relief. Take the case of headache. While not every case of headache is of sinus origin, careful study should be made definitely to rule the sinuses out as a cause. Some individuals are able to bear pain and carry on their work despite severe headache. When a sinus headache is great enough or continuous enough to prevent the individual from leading a satisfactory existence, this relative indication is for radical operation, other means of relief having failed.

Profuse discharge, anterior or posterior in type, may cause a day laborer little inconvenience, while to a preacher, a public speaker, a teacher, a physician, a society woman, or many another, the annoyance will be intolerable. Nasal crusting, which is dried discharge, comes in the same category, and discharge accompanied by an obnoxious odor is also a relative indication, depending upon the amount of annoyance caused. Comparatively few patients are themselves conscious of the odor in their own noses, and it is therefore in this instance the effect of this odor upon those with whom their daily occupation brings them into contact that must be considered. Its inconveniences

the companions of the ditch digger but little, but for the rhinologist or the dentist it may account for his failure to win or maintain a paying practice. Pain as distinct from headache, when sufficiently intense, calls for sinus surgery. Major tics and "habit" pain must be carefully ruled out. Indeed hospitalization with a thorough study from all angles, must usually, except in emergencies, precede the decision to operate radically. General ill health dependent upon sinus disease becomes a deciding factor in favor of radical operation when other methods of relief have failed, other causes have been eliminated, and the attending physician feels that something more must be done to remove or control the focus of infection. Many of us will admit that at times nephritis, arthritis, carditis, chronic cough caused by enlarged mediastinal glands, bronchiectasis, certain allergies (bacterial), gastro-intestinal disturbances in adults as well as infants, malnutrition, malaise, and many other general conditions may be attributed to sinus infection. Not a few follow Emerson, in believing that the progress of certain cases of advancing deafness is dependent upon sinus infection, even with scanty or absent discharge, while the ophthalmologist tells us that many eye disorders, recurrent iritis, uveitis, iridocyclitis, keratitis, and certain difficult errors of refraction cannot be satisfactorily handled by him without the help of the rhinologist. True, conservative treatment often suffices, but when that fails, radical operation is indicated, not as a life-saving measure but as one looking toward the preservation or restoration of function.

After all is said and done, a thorough study of the case and a correct diagnosis is the first requisite for deciding upon the type of treatment, and no radical surgery should ever be done without this preliminary, although in emergency the study should be intensive. Having made this study and diagnosis, the careful surgeon will then determine in his own mind that type of treatment or operation, or succession of operations, which his own experience or the experience of others in whom he has faith leads him to believe will do his patient the utmost good, but he will not undertake radical surgery without a thorough knowledge of the anatomy and applied anatomy of the parts under consideration and unless he has also had a careful and thorough training in the procedure and technic required

for such surgery. These points have again and again been made by such eminent students of the accessory sinuses, their anatomy and surgery as Fenton, Hajek, Skillern, Mosher, Sluder, Tilley, Lynch, Sewall and many others.

CLINIC OF DR. CHEVALIER L. JACKSON

FROM THE DEPARTMENT OF BRONCHO-ESOPHAGOLOGY OF
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ACUTE LARYNGOTRACHEOBRONCHITIS IN CHILDREN

ONE of the many contributions of modern medicine to humanity is the removal of diphtheria from the category of fearful plagues and placing it in the class of curable and preventable diseases. It is to be regretted, however, that this great good fortune for mankind contributed to the overlooking of another disease, one that has many of the clinical features of diphtheria, and which is now more often fatal than diphtheria because we have no remedy for it that is in any way comparable to the curative effect of diphtheria antitoxin. This does not mean that nothing can be done for acute laryngotracheobronchitis. On the contrary the percentage of mortality can be greatly reduced by proper care and management.

The disease laryngotracheobronchitis was well known to Bland and the other leading French physicians as nonmembranous laryngotracheitis, a century before the bacillus of diphtheria was discovered, and that remains today the outstanding characteristic of the disease: It presents the clinical picture of laryngotracheobronchial diphtheria but it is not diphtheria. Since the days of Bland we have learned how to cure and even prevent diphtheria whereas nondiphtheritic acute laryngotracheobronchitis remains one of the most fatal acute infections of very young children. Though we have no specific cure for it that compares in any way with diphtheritic antitoxin for diphtheria, yet we have learned much about the disease and are able to save many lives by modern methods of treatment.

There is, as you all know, a common form of acute respiratory infection of the air passages that is prevalent every winter; but in addition to that we have this fulminating acute laryngotracheobronchitis that has so many distinctive clinical features that it seems to be a definite clinical entity rather than simply a severe case of the same disease. The general clinical picture is that of diphtheria rather than of the ordinary acute respiratory infection.

Etiology.—The etiology of the disease is interesting. Undoubtedly all the cases are infective. It is, however, not always the same organism that is found predominant. Over 85 per cent of our cases have been unquestionably streptococcal. Although the disease usually occurs when influenza is prevalent the bacillus of influenza has been found predominating in only about 5 per cent of the cases, and in most of these the influenzal organism was soon superseded by streptococci, occasionally staphylococci. Dr. J. H. Font informs me that in his experience a staphylococcus is the predominant organism in typical cases of acute laryngotracheobronchitis occurring in Puerto Rico.

Symptoms.—You are all familiar with the symptomatology of laryngotracheobronchial diphtheria, the hoarse voice, the croupy cough, the effort to breathe contrasting with general apathy, the toxic appearance, the preference for remaining in bed and especially that impression the experienced physician gets that the child is potentially a very sick child, out of proportion to the graphic charts and laboratory reports. Soon there develops evidence of respiratory trouble, the breathing is no longer quiet and noiseless. A slightly audible wheeze is heard at the open mouth; the participation of the accessory thoracic muscles is more noticeable than normal; there is pallor, not cyanosis. Soon the efforts of the accessory muscles become more pronounced; there is retraction at the suprasternal notch, in the intercostal spaces, and at the epigastrium. The child becomes less apathetic and more restless because of air hunger; he wants to be taken up, because in his mother's arms he can use his accessory respiratory muscles to better advantage. The difficulty in breathing, which up to this time has been inspiratory, becomes also expiratory; the wheeze increases and becomes stridorous; the skin may be cyanotic

but more often it is ashy gray. Every time the little patient starts to fall asleep he suddenly awakens with a start, because as soon as the unconsciousness of sleep approaches he loses the voluntary aid to the muscles of respiration and he starts to asphyxiate. He is so drowsy from loss of sleep that he can hardly keep his eyes open, but instinctively he dare not go to sleep. If tracheotomy be not done he will soon give way to the overpowering need for sleep and he will quietly but suddenly go to sleep for the last time.

This clinical picture fits the symptomatology of both acute laryngotracheobronchitis and diphtheritic laryngotracheobronchitis equally well. The *physical signs*, on examination of the chest in the two diseases, are in a general way the same.

Differential Diagnosis.—How, then, is the differential diagnosis to be made?

The two diseases are quite different in the findings of both objective and bacteriologic examinations and in the progress of the respective illnesses under treatment.

In almost all cases of diphtheria no physician who has ever seen the membrane could fail to recognize diphtheritic membrane in the fauces or pharynx; the difficulties arise when there are hoarseness, croupy cough and noisy respiration without membrane visible on ordinary inspection in these regions. There may not be even a very intense pharyngitis and secretions from the pharynx may be negative bacteriologically.

How can the differential diagnosis be made between acute laryngotracheobronchitis and laryngotracheobronchial diphtheria in such cases?

The differentiation rests upon the exclusion of diphtheria of the larynx and tracheobronchial tree. To do this with certainty requires direct laryngoscopy and, if the larynx be negative, bronchoscopy.

If at direct laryngoscopy membrane is seen in the larynx and swab specimens from the interior of the larynx show the presence of diphtheritic bacilli the diagnosis of diphtheria is definitely made. If, however, there is no membrane, only intense inflammation and subglottic edema, and the swab specimens show no diphtheritic bacilli, we must examine deeper. A bronchoscope is put in; if the mucosa of the trachea shows only inflammation and the bronchoscopic swab specimens are

negative we may exclude diphtheria. In the tracheobronchial tree, as in the larynx, this definitely negative conclusion is justified only after the expiration of six or seven days from the first symptoms. If the disease is diphtheria, membrane and the specific bacilli will surely be in evidence by that time; usually before.

Some of you may be located far from the medical centers where bronchoscopy is available. How shall the diagnosis be made under such circumstances? It is best to give diphtheritic antitoxin. If the disease is diphtheria improvement will be noted within forty-eight hours. If the disease is nondiphtheritic laryngotracheobronchitis tracheotomy will be required to prevent asphyxia. Swab specimens from the trachea will then be available for bacteriologic decision.

By exclusion then we reach the diagnosis of acute laryngotracheobronchitis.

Bacteriologic Diagnosis.—Next in importance comes the bacteriologic diagnosis. This has usually been already indicated in the reports of the bacteriologic search for diphtheritic organisms. Most frequently the predominant organism will be a streptococcus and often it will be in nearly pure culture.

Complications.—One of the most important clinical features of laryngotracheobronchitis is the serious character of its complications. Prominent among these is infection of the blood stream. This is especially frequent in the streptococcic cases but it does occur in the other infections also. The not infrequent visceral complications are endocarditis, pericarditis, acute myocardial degeneration; toxic degeneration of liver, spleen, kidneys; pulmonary infarct, hemorrhagic lobar pneumonia. The most frequent of all complications is subglottic edema of the larynx requiring tracheotomy. Ordinarily this is only a mucosal edema; but in some of the cases, especially the streptococcic, laryngeal perichondritis, abscess, chondral necrosis and subsequent cicatricial laryngeal stenosis are complications. Next in seriousness is bronchopneumonia. Less frequent but equally serious is pulmonary abscess.

Bronchopneumonia is a dreaded complication but we must guard against allowing our fears to mislead us into mistaking areas of atelectasis for areas of pneumonic consolidation.

Over and over again we have seen the areas of impaired percussion note supposed to be pneumonic become normally resonant after the aspiration of the obstructing thick viscid bronchial secretions through the soft catheter in the hands of

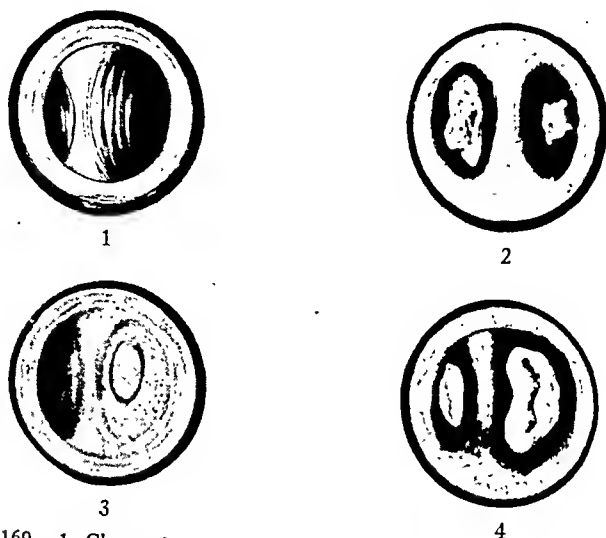


Fig. 169.—1, Charcoal sketch of normal, widely open right and left bronchial orifices, as seen through the bronchoscope. The carina is thin and sharp; the rings are visible through the thin, smooth, normal mucosa. (The color of normal mucosa is a delicate pink.)

2, Bronchial obstruction as seen through the bronchoscope in laryngotracheobronchitis. Both bronchial orifices are obstructed by crusts. The mucosal swelling narrows the orifices, broadens the carina and obliterates the rings. The crust in the left orifice obstructed it completely, causing atelectasis of the left lung. The crust on the right acted as a check valve producing obstructive emphysema in the right lung. The color of the swollen mucosa was mottled bright red. The color of the crusts was brownish.

3, The right bronchial orifice is occluded by swollen mucosa except for a small central opening and this is occluded by pus. It was noted that the pus was not wafted in and out, which is positive evidence of complete obstruction. This had produced an atelectasis of the right lung which had been mistaken for consolidation.

4, Exfoliating casts of membrane is tracheobronchial diptheria. The whitish casts were in strong contrast to the dark crimson, swollen mucosa.

a nurse, or after the removal of a crust or plug of gummy secretion from a bronchial orifice.

Prognosis.—The disease under consideration is a very serious one, more serious than promptly recognized laryngeal

diphtheria under treatment by antitoxin. The mortality of fulminating streptococcic laryngotracheobronchitis in some winters was as high as 70 per cent and seldom fell below 50 per cent until recent years. Under modern methods of treatment probably the best that can be done is to lower the mortality to 25 per cent. Blood-stream infection is always of most serious prognosis. Bronchopneumonia is of more serious prognosis as a complication of this disease than under any other circumstances. Cardiac and other visceral complications usually are fatal.

The following case reports are typical:

Case I. Acute Laryngotracheobronchitis of Moderate Severity.—A boy, three and one-half years old, was admitted with a history that two days before he had had a sudden attack of choking, wheezing and dyspnea. Adrenalin had been given without benefit on a tentative diagnosis of asthma. There had been slight nasal discharge for a few days prior to the onset of choking and wheezing. Diphtheria antitoxin had been given though bacteriologic examination had been negative for diphtheria. On admission the child was extremely dyspneic, and toxic; temperature, 104° F. On direct laryngoscopy the larynx was found acutely inflammatory; a large quantity of thick viscid secretion was visible in the trachea. A slender aspirating tube was inserted through the laryngoscope and the viscid secretion was aspirated. It contained many hemolytic streptococci; also hemolytic staphylococci. The endotracheal aspiration gave temporary relief; but the secretion reaccumulated in a half hour, with return of the extreme dyspnea. Tracheotomy was then done and catheter aspirations were done frequently by the nurse. The air of the room was kept moist, no sedatives and no atropine were given. Improvement followed; the secretions became less viscid. Two weeks later, after the corking-of-the-cannula test, the child was decannulated and, on the eighteenth day, discharged.

Comment.—This case is a good example of early diagnosis, and of the treatment we have found most efficient: namely, prompt tracheotomy, catheter aspiration by the nurse, abundant fluid by mouth, moist air, rest, quiet, avoidance of atropine and sedatives that thicken secretions and promote crusting and bronchial obstruction.

Case II. Acute Streptococcic Laryngotracheobronchitis; Severe Fulminating Type.—A female child, aged fourteen months, was sent to the clinic for tracheotomy. Her condition was urgent; her color was ashy gray; she was obviously almost dead of asphyxia; there was deep indrawing at the supra-sternal notch, the epigastrium pulled inward in funnel form. Direct laryngoscopy showed the glottis almost completely closed by red subglottic swell-

ings on each side. A small bronchoscope was insinuated to maintain respiration while tracheotomy was being done, it was immediately clogged with thick secretion; this and the trachea below it were cleared by aspiration. The child fell into a sound, quiet sleep on the table. Her temperature was 102° F., pulse 110, respirations 32. She was carried to a tented crib into which steam was supplied by an electric vaporizer. Viscid secretions were aspirated at short intervals by the nurse using a child's size soft-rubber catheter passed through the cannula. The patient eagerly swallowed milk and water when she awakened, but she spent most of the first twenty-four hours in sleep. On the second day she took interest in her surroundings and played with her toys. On the third day she became restless. The nurse had been cleaning the inner cannula at short intervals, but the breathing this time did not seem clear. We took out the cannula and found it unobstructed; we spread the wound with the Trouseau dilator and found the passage to the trachea clear. We noted a slight wheezing sound in the respiratory air current. We put in a bronchoscope. The mucosa of both main bronchi was swollen and their lumina were obstructed with thick viscid secretion. The bronchoscopic aspirator removed the obstruction. Again the child took nourishment and an interest in her playthings. Before long, however, she became pale, listless, then restless. Physical examination of the chest showed the breath sounds had disappeared from both bases and the percussion note suggested beginning double basal lobar pneumonia. Knowing that this usually means obstructive atelectasis we put in the bronchoscope. After aspirating viscid secretions we went on down the right bronchus and found the lower lobe bronchus, just below the middle-lobe bronchial orifice, occluded by a dried, gummy plug of secretion. We removed it with bronchoscopic forceps. Bronchoscopic exploration of the left side revealed the left lower-lobe bronchus obstructed in the same way as the right lower-lobe bronchus, and we removed this obstruction in the same way. After the bronchoscopic clearing of the airway the patient went into a deep, quiet, restful sleep. When she awakened she again took an interest in her surroundings. During the second week there were many repetitions of this cycle of restlessness, pallor, appearance of approaching death, obstructive atelectasis simulating pneumonia; each attack was relieved by bronchoscopic removal of obstructive material from the bronchi. But the patient had not been gaining generally. We were relieved to find blood cultures negative; the blood picture was that of severe anemia. Every detail of medical care and management was carried out under the supervision of Doctor Ralph Tyson and his pediatric personnel. At the end of the third week slight improvement was noted and in the fourth week convalescence was established.

The first secretion removed showed pure culture of hemolytic streptococci, and throughout the illness these organisms predominated.

Comment.—This case is typical in the severity of a primary attack of respiratory infection; the cardinal signs of obstructive laryngeal dyspnea demanding tracheotomy; the secondary attack of dyspnea from bronchial obstruction; the repeated attacks of dyspnea simulating pneumonia but completely and

immediately relieved, at first by catheter aspiration, later by bronchoscopic removal of crusts and plugs of dried secretion obstructing the bronchi. In cases of this degree of severity the mortality is high, especially so when there is a blood-stream infection.

Treatment.—Now let us consider the essentials in the treatment of nondiphtheritic acute laryngotracheobronchitis. The primary and the fundamental requirement is the maintenance of an adequate airway on which the patient's life depends. More mortality has resulted from inadequate "plumbing," one might say, than from any other one cause. By plumbing in this connection we mean the maintenance of clear tubes, artificial and natural, all the way from the nose and mouth to the pulmonary air cells. The cardinal sign of obstruction to the airway, regardless of location, is restlessness. It cannot be too emphatically stated that restlessness in a child with acute laryngotracheobronchitis means air hunger and to give him sedatives means death. Although sleepy, he is doing his best to stay awake in order to get the help of his voluntary muscles of respiration to pull in air through obstructed passages. Opiates will rob him of his natural defense in his fight for life. One has only to look at the indrawing at the suprasternal notch to see how hard he is pulling. If tracheotomy be done he will fall into a quiet, restful sleep without opiates; his color will return and when he awakens he will accept the food and water that, before, he refused because he dare not stop long enough in his fight for air. He will take an interest in his toys. At intervals the nurse puts down through the cannula a child's size soft-rubber catheter attached to the aspirator and thus removes the thick viscid secretion in the bronchi that otherwise would thicken and obstruct the bronchial lumen.

In more than half the cases permanent relief results from tracheotomy, followed by proper after-care and frequent catheter aspirations of the viscid purulent secretions from the tracheobronchial tree by the nurse, every time the sound indicates the presence of secretions. The breathing through the cannula when it and the natural lower air passages are clear is a soft blowing sound audible only when the ear is near the cannula. The after-care of the cannula includes frequent

removal and cleansing of the inner cannula by the nurse; removal and change of both inner and outer cannulae by the physician, daily or oftener. The dressings are changed by the nurse as often as soiled, a number of times daily.

In more than a third of the cases there comes a time when catheter aspiration by the nurse does not give the relief it did at first; the clear soft blowing sound of breathing is not restored. The child becomes restless; the restlessness increases; the child no longer takes an interest in anything. Again I repeat we should beware of sedatives; this restlessness means air hunger. Nothing but bronchoscopic removal of bronchial obstruction will relieve it.

Next in importance to maintenance of a clear airway comes guarding against dehydration. This condition is not only dangerous in a general way but it favors viscosity of bronchial secretions. The pharyngeal and faucial inflammation renders swallowing painful in the earlier stages, later the child may be either too toxic to ask for water or too much occupied with his fight for air to stop long enough to drink water. The best method is for a watchful nurse to put cold clear water of good quality into the child's mouth with a medicine dropper in small quantity at very short intervals. A little will trickle down each time and be swallowed. By good quality I mean to exclude a chlorinated city water reeking with flavor of the operating room sterilizer. Moisture of the air in the room is vitally necessary not merely as lessening dehydration but in diminishing the drying effect of the inspired air on bronchial secretions. The air in the room should be kept at the dew point. In this connection it is necessary to remember that in winter when the outside air is at, say, zero, it holds very little water even if saturated; and when this air is heated by our modern heating systems to, say, 70° F. it is so dry as to be almost cauterant to the bronchial mucosa of a tracheotomized child. Moreover, it quickly desiccates bronchial secretions into a gummy material that acts like a rubber stopper in a bottle. The most convenient means of moistening air is with an electric vaporizer, but in its absence an open vessel kept constantly boiling is quite efficient. Additionally a few minims of sterile water may be dropped into the tracheal cannula with a medicine dropper by the nurse before each catheter aspiration.

I have mentioned the danger of giving sedatives of any kind, but especially opiates, to a child who is restless because of air hunger. There is another dangerous effect of such medication; it thickens and thus renders more obstructive the already viscid inflammatory bronchial secretions. Belladonna has the same effect. Over and over again the bronchoscopic observations have demonstrated this. They have also demonstrated another injurious effect of opiates and other antitussive medicaments: namely, inhibition of the cough that is part of the normal defensive drainage mechanism of the lungs. "The cough reflex is the watchdog of the lungs" is an axiom in our clinic department.

In conclusion I should like to call your attention to the fact that in the treatment of children with acute laryngotracheobronchitis the physician is confronted with a toxic disease which though self-limited is usually of much longer time limit than diphtheria. The heart is trying to keep going notwithstanding that its innervation is weakened from overstimulation of prolonged carbon dioxide excess, its musculature is weakened from the same cause and, additionally, there is toxic dissolution of the muscle cells and usually also a myocarditis. It is appalling to see that feeble, struggling heart called upon for what may be a fatal effort to go through endless examinations and unnecessary attention. There are two things necessary to save life, namely, water and a clear airway. Next in importance is to conserve the child's strength in every possible way. Only the most vital attention should be given. The child needs rest and quiet to maintain his resistance at the highest possible point. Examinations should be as few as consistent with proper care and management. Uncomfortable methods of treatment should be avoided when not absolutely indispensable. Everyone, family, nurses and physicians should have constantly in mind the motto: "Don't wear the baby out."

CLINIC OF DR. ROBERT F. RIDPATH

TEMPLE UNIVERSITY MEDICAL SCHOOL

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ACCESSORY SINUS DISEASE

I THOUGHT, today, we would take up some of the symptoms and diagnostic points of accessory sinus disease which are commonly present, and which you, I hope, may find of value in your work. If the symptoms of all diseases were clear-cut and always present, medicine would indeed be easy to practice. Instead we always have the human element, with its peculiarities, to consider and thus few of the typical symptoms may be present and yet the patient may be in a precarious condition. It is unfortunately a fact that the symptoms of some infections or malignancies of the accessory sinuses are so obscure and clouded that it requires a rhinologist of considerable experience to make a complete and true diagnosis.

Generally speaking empyema of the accessory sinuses has not only the visual sign of pus from various parts of the nose and epipharyngeal space but has also all the associated symptoms (of pus) found elsewhere in the body, *i. e.*, fever, pain, swelling of tissue, lassitude, malaise, anorexia, etc.

The causes of empyema of the accessory sinuses are numerous with perhaps repeated colds, with a predisposition to grippe, being the most frequent factor. Other causes may be allergy, inheritance of specific type of membrane or bony framework, trauma, foreign bodies, croupous pneumonia, diphtheria, scarlet fever, measles, smallpox, tuberculosis, typhoid fever, cerebrospinal meningitis, etc.

There are several processes by which these cavities with their covering of mucous membrane may become diseased and these may be considered in the following rotation:

- (a) Through direct invasion of the sinus by bacteria.
- (b) Through extension of infection or inflammation from adjacent parts.

- (c) Through the blood and the lymph channels.
- (d) Through traumatism.
- (e) Through exposure to cold or chilling of the body.
- (f) Through swimming and diving.
- (g) Through foreign bodies.
- (h) Through nasal blockage from benign or malignant tumors.

Although there are many symptoms which are characteristic of an infection of any or all of the sinuses I think it might clarify our subject if we would take the symptoms of infection of each sinus separately.

Maxillary Sinus.—Let us first speak of the maxillary sinus. This sinus as you are aware is located in the maxillary bone, is present at birth and continues enlarging by resorption of bone and internasal pressure throughout life. At the age of ten or twelve years the floor of the sinus is on a level with the floor of the nose and from this time on it extends downward and backward. With continuous resorption of bone throughout these years occasionally the anterior and possibly the orbital bony wall are entirely absorbed. The ostium, as I have pointed out in my former talks to you, is in the anterior and superior portion, and by its location is a decided factor in the periodicity of the symptoms of disease of this cavity.

The first symptom of empyema of any of the sinuses that we should consider is pain, and this, of course, holds true in this sinus. In my experience very few cases have come under my observation without this symptom. The character of the pain is dull and sickening, the periodicity (due to the position of the ostium) is after the individual has been in the upright position for some time or about 10 or 11 o'clock in the morning. This pain increases in severity as the day advances until the pus has increased to such an extent that sufficient pressure is exerted on the swollen membrane at the opening or ostium, when we have an outflow of the material into the nasal cavity. The position of the pain is also characteristic inasmuch as we find it at the supra-orbital notch and at the inner canthus of the eye on the side affected. Seldom do we have pain over the sinus itself and when this does occur we may be sure that bone is involved. We may also on occasion have pain in one or more

teeth or a feeling as if the first or second molar is too long; this is due to the roots of these teeth being in close proximity to the cavity. The second symptom is fever and this also occurs or increases during the daytime so that although our patient may feel fairly well when he first arises in the morning, as time passes he becomes distinctly worse. Vertigo may be a condition of quite some moment, this perhaps more pronounced when the patient stoops forward. Anorexia, malaise, nervous excitability and a general feeling of prostration are all associated and mentioned by our patient. He will also in all probability give you a history of blowing or expelling a considerable quantity of purulent discharge from the nose the first thing in the morning. This, as you can realize, is due to the sinus draining and emptying itself during the night.

Examining the patient by dilating the nostrils with a nasal speculum we find the mucous membrane of the side affected swollen, red, and more or less pus in the inferior nasal passage and if we look further we notice that there is a line or string of this discharge coming from the hiatus semilunaris or from under the anterior portion of the middle turbinate and covering the membrane on the middle turbinate anteriorly. Should this specific case be of long standing and in a chronic condition then we may have an extension of the inflammatory symptom to the eyes with redness, burning and interference of lacrimal drainage.

Empyema of the maxillary sinus must be differentiated from malignancy of this sinus as well as from dental cysts. A positive diagnosis is easily made by a lavage of the sinus, but before any operative measures for the cure of a persistent or chronic infection be attempted an x-ray study from various angles should be made.

Frontal Sinus.—And now suppose we consider the main symptoms of a frontal sinus involvement. Although all infections of the sinuses must be considered from the standpoint of the length of time of the infection, this is particularly so when dealing with the frontal problem.

The development of this sinus is much later than that of any of the other cavities associated with this subject. Generally speaking it is formed by an anterior ethmoid cell pushing its way between the two plates of the frontal bone. This according to

some authorities begins at three or four years of age but more frequently associated with a later period of six or seven years of life. This later development of the frontal sinus immediately informs us that children very seldom, if ever, have infection of this cavity.

Later in life, due again to the absorption of bone and internasal pressure, we have the sinus increasing in size and extent, so that it may involve the whole frontal bone and, as a matter of fact, extend laterally to the parietal and temporal junctions.

The ostium is in the most inferior portion of the sinus. When we are in the upright position (sitting or standing) we are, therefore, in the best possible position for drainage of the cavity, but we are in the worst position when we are lying down or in the recumbent position. This is the exact opposite of the maxillary sinus for whereas our patient is relieved by his position in bed in the antral infection, his symptoms and difficulties increase in that position when the frontal sinus is involved.

One must also realize that due to the posterior wall of this cavity being thin and perforated by innumerable openings through which the lymphatics of the dura penetrate to ramify through the mucous membrane of the sinus the danger of involvement or extension to the meninges and brain is ever present.

The enumeration of the symptoms is taken up in a way similar to those we have already mentioned. First pain; this is over the frontal area; closely associated with the orbital ridge and extending upward toward the vertex. It again is sickening and dull in character and is decidedly aggravated by smoking or drinking of alcoholic liquors. It is also increased by bending forward and, as a matter of fact, the vertigo or dizziness may be of such a severe character that the patient may fall. It is also, as stated before, increased by assuming a prone position or by pressure over the affected area. Pain in the eye, or eyes, is frequently encountered. Fever is present and this increases as the cavity fills, causing pressure and increased absorption of toxic material. Malaise, anorexia, nervousness and a general feeling of prostration is apparent. I am stating the symptoms of the acute variety as these are the cases we

see more of and essentially are those requiring immediate attention. A very important visual sign, meaning danger, is the swelling of the upper eyelid with edema of the conjunctiva and dislocation of the eyeball downward and outward. Should this be present immediate opening of the sinus is indicated.

Inspection of the nasal cavity may or may not show a purulent discharge. Should the infectious material be of a thick, tenacious character, the closure of the ostium preventing drainage and aeration may be complete, and no discharge may be discernible. Swelling and congestion of the mucous membrane is quite pronounced and extensive, and olfaction may be interfered with.

Certain conditions may simulate frontal sinus disease and should be differentiated and it is better to tabulate them than to use the ordinary method of note taking.

Frontal Sinus Disease

Usually a history of cold or grippe.
Pain, mild at first becoming more severe.
Pain continuous.
Pain intensified by pressure.
Coughing and sneezing intensify pain.
Alcohol and tobacco increase pain.

Supra-orbital Neuralgia

No such history.
Pain, short and lancinating.
Paroxysmal in character.
Pain relieved by pressure.
No effect.
Not so.

Mucocele of the frontal sinus generally occurs in middle life. There are no subjective symptoms until the swelling from the enlarging mass becomes apparent and we then have pressure symptoms. There is no nasal discharge and the patient is only cognizant of something wrong by the tumefaction over the frontal area, frequently with orbital dislocation. There is no fever or toxic symptom present. Malignancy is more apt to occur later in life or past the meridian. The subjective symptoms are progressive and we have a fetid, disagreeable nasal discharge in the majority of cases. Increasing dilation of the sinus is also a fairly constant sign as is gland enlargement, etc.

Many other diseases may affect this cavity and although tuberculosis is considered rare, nevertheless it does occur. Syphilis seems to have a predilection during the third stage of the disease for the anterior plate of this sinus and a complete serological study with repeated x-ray examinations should be

made. Osteomyelitis, meningitis, sub- and intradural abscess may all be associated or the result of infection or empyema of this sinus and it behooves us to be as careful in our diagnosis and treatment as possible.

Ethmoid Sinus.—The ethmoid sinus although considered as an accessory sinus is not accessory, nor is it a true sinus in the full sense of the term. It lies within the nasal chamber and consists of a capsule which contains a number of cavities or cells separated by thin bony divisions. Its position is the space between the cribriform plate of the ethmoid and the lamina papyracea. It is present in practically its permanent position, but is slightly smaller in size, at birth. Embryologically it develops in the grooves between the ethmoturbinates and as early as the third month of fetal life crescent-shaped folds break the evenness of the primitive lateral nasal wall. This is the rudiment or anlage of the processus uncinatus and is the first of a series of accessory folds to appear on the lateral wall of the meatus. This fold aids in forming a furrow immediately superior to it—the primitive infundibulum. Shortly after this we have the first evidence of the bullae ethmoidales.

To understand the reason for various symptoms pertaining to disease of this sinus, I feel it would be wiser for us to review to a limited extent a few points in the anatomical arrangement of these cells.

The construction of the ethmoidal labyrinth is perhaps better understood if we consider it as a cube. This elongated box is then divided unevenly into two distinct divisions by a bony partition. We thus have an anterior and a posterior part. Now divide the anterior portion into other portions (two or three) and these portions or cells connecting with a groove or furrow (the infundibulum), and we easily visualize this part of the ethmoid capsule. The posterior portion is now divided into several unequal parts and these represent the posterior ethmoidal cells which connect or have their aeration and drainage through the superior nasal passage. We are now in a position to realize that any pus due to disease of this capsule will necessarily have to appear in two places: that from the anterior division into the infundibulum thus into the anterior part of the nasal chamber; and the discharge resulting from a diseased condition of the posterior cells into the choana and epi-

pharyngeal space, thence into the throat or on the pharyngeal wall.

Disease of the ethmoidal sinus may be divided into the acute and chronic inflammations, and these are again divided into the acute catarrhal inflammation; the acute suppurative; the chronic catarrhal or hyperplastic ethmoiditis; the chronic suppurative or empyema; and the chronic catarrhal inflammation with suppuration. The symptoms of acute catarrhal inflammation are those which occur to a greater or less degree with an attack of acute coryza, or cold, depending upon the length and severity of the attack. The whole ethmoidal labyrinth becomes swollen and edematous. Frequently there are punctiform hemorrhages on various parts of the surface, particularly the mucous membrane covering the anterior portion of the middle turbinate. The congestion and edema thus closing the nasal passages and essentially causing an inability to breathe properly; the whole nose, or especially the space between the eyes, feels stuffy and full. Headache over the brow, between the eyes and pain on movement of the eyes are quite pronounced. Fever and a general feeling of decided discomfort is definitely distressing. Dry tongue and dry mouth, due to mouth breathing is a frequent symptom. In the acute purulent type, symptoms are similar but due to the formation of thick tenacious discharge, they are more severe in nature. Whereas in the acute catarrhal type we may have some nasal breathing, in this purulent type there is practically always absolute occlusion of the nares. Headache is, of course, constant with periodical neuralgic outshoots toward the deeper structures of the eyes. Decided pain on rotation, epiphora, orbital neuralgia on reading or otherwise concentrating the gaze. Loss of smell, taste, and appetite, with constipation and vertigo associated.

In chronic inflammation of the ethmoid labyrinth the condition resembling chronic coryza predominates. Every exposure to cold, draughts, chilling or damp feet produces attacks of sneezing. Increased secretions from the nose, watering of the eyes, and other ocular manifestations are present. Associated with these prodromal symptoms we have headaches situated between the eyes, over the parietal region radiating toward the vertex, these becoming a constant factor. Stooping

and jarring increase these pains, as do indulgence in alcohol and tobacco. A marked feeling of fulness is present in the ethmoidal region and intra-ocular pressure may be present.

Disturbance of olfaction or the sense of smell is common. The exudate or secretion is abundant, acid, and slightly yellow in color. Due to mouth breathing and stagnation and fermentation of the secretion an unpleasant or musty taste in the mouth is characteristic.

Vasomotor disturbances such as edema of the eyelids or hyperemia of the conjunctiva may occur. Continuation of this condition is very prone to produce nasal polyps with all their symptoms of nasal occlusion, etc.

Empyema or chronic suppurative inflammation is always due to bacterial infection. Changes in the mucous membrane are similar to those which take place in the larger sinuses. Round cell infiltration with proliferation of the epithelium occurs, this may be of such moment to entirely occlude the ostium of some of the cells.

Chronic hyperplastic inflammation with suppuration. This condition is the result of constant drainage of a purulent secretion over a given area of nasal mucosa which sooner or later gives rise to polyposis. This would essentially give us all the symptoms which we have enumerated in the other classifications; however, the complications arising from this condition are more numerous and of a more severe or dangerous character. Due to the chronicity of the condition and consequential softening of the tissues, an external rupture with fistula formation is the most frequently met with. The point of predilection for this fistula to occur is in the region of the ethmolacrimal suture. This same fistula formation is sometimes met with in children and wrongly diagnosed.

Perhaps the next most frequent complication is the rupture into the orbital or bulbar cavity. This is characterized by sudden outward dislocation of the bulb, swelling and infiltration of the eyelids, intense pain in the eye, fever and general prostration.

Inflammation of the lacrimal duct can and does occur either by direct extension of the infection or by venous return carrying infection from the cells to the lacrimal canal or sac.

Intracranial complications with meningitis or abscess for-

mation can readily result from direct extension or through the ethmoid veins. The more common manner, however, seems to be through the sheaths of the olfactory nerves, and thence through the cribriform plate direct to the meninges. Cavernous sinus thrombosis with all its symptoms may result from direct infection of the ethmoidal veins which empty into the ophthalmic veins and thence into the cavernous sinus.

Perhaps it would be apropos to tabulate the difference between the chronic hyperplastic type and the chronic purulent type.

Chronic Hyperplastic Ethmoiditis

Usually bilateral.
Secretion clear and watery.
Never crust formation.
Headache most prominent symptom.
Ophthalmic manifestations due to pressure of hypertrophic mucous membrane on vessels.
Gastric disturbances absent.
Neurasthenic symptoms predominate.

Chronic Purulent Ethmoiditis

Usually unilateral.
Secretion purulent.
Always crust formation.
Headache light, seldom severe.
Ophthalmic manifestations due to infection from purulent secretion and toxemia.
Gastric disturbances frequent.
Neurasthenic symptoms not marked if flow of secretion is free.

The Sphenoid Sinus.—This, the last of the accessory sinuses of the nose. In anatomical relationship it is somewhat different from the other sinuses inasmuch as up until the third year it is nasal in position, rather than sphenoidal, and it is after this period that the rudimentary sinus is surrounded by bone rather than the ostium enlarging into a sinus through resorption of the sphenoidal body, which takes place much later in life.

The adult sphenoid sinus is a cavity directly in the body of the bone and occupies almost a central position in the skull, varying in size according to its development. Should the resorption and the pneumatization continue very large sinuses with walls of extreme thinness may result and we can readily understand the orbital and cranial complications, the result of empyema, occurring from these cavities.

Of the six walls, the most important rhinologically is the anterior. This so on account of having the ostium, which is situated in the upper third of this wall, and by which we may enter the sinus for drainage and treatment.

Closely associated with the superior wall we have the right and left optic nerves and the optic chiasm. Above or slightly posterior, the coronary sinuses and the pituitary body which occupies the sella turcica.

The external wall helps to form a portion of the middle cerebral fossa and is, therefore, in direct communication with the cavernous sinus and the internal carotid artery. Unfortunately as the sinus increases in size, this, the external wall, becomes thinner and thinner, sometimes disappearing entirely, leaving only the periosteum or a dehiscence in place. Numerous perforations or openings are formed for the passage of small venous capillaries which anastomose or empty directly into the cavernous sinus. Thus situated, as it is, the sphenoid sinus occupies a position which, when diseased, may and does give rise to a complexity of symptoms.

The symptoms of this as in the other accessory sinuses are spoken of as subjective, objective and ocular. Under the subjective we have pain, inability to concentrate, forgetfulness, aversion to mental or physical work, cough, lassitude or malaise, anorexia, lack of interest, vertigo, etc. Under the objective we put discharge, cacosmia, crust or pus on the pharyngeal wall with probably a more or less proptosis. The ocular symptoms might be an enlargement of the blind spot, retrobulbar neuritis, scotoma, either scintillating, spot, hair, or the feather varieties.

In speaking of the symptoms of sphenoidal infection, let us first consider those associated with our first division or the subjective.

Pain.—This phenomenon may be divided into various forms of headache due to pressure, reflex or toxic manifestations. It mainly depends upon the pathological condition present within the sinus. Pressure, whether the result of congested and swollen membrane impinging on its fellow membrane, or through a tenacious, mucilaginous pus filling the cavity and occluding the ostium, is likely to give symptoms of a similar nature.

The headache is mainly situated in the occipital region, radiating in fan-shape upward toward the vertex. Reflex pain of toxemia or other origin may extend over the mastoid region, simulating in character and severity acute mastoiditis. This

pain accompanied frequently by considerable muscular stiffness in the neck muscles may extend downward toward the clavicular region or even as far as the humerus-scapular-clavicular articulation.

Pain back of the eye of a dull character giving a feeling of pressure exerted from behind forward, which is not increased by pressure made over the eyeball or lids is almost pathognomonic of sphenoidal infection.

Vertigo.—This is present either in a continuous or interrupted nature and is manifested whether the patient is in a recumbent or upright position, and may be so pronounced and distressing in character as to cause a fall.

Sleeplessness.—In spite of the general and sometimes profound toxemia present the majority of sufferers from sphenoidal infection are unable to sleep with any degree of comfort.

Cough.—This most persistent symptom and annoyance is always present; is spasmodic and of a throaty character.

Malaise.—Malaise and forgetfulness with inability to concentrate or take interest in one's surroundings or work or play are symptoms usually elicited.

The objective symptoms are few and mainly consist of congested postethmoidal mucous membrane and swollen tissue in the spheno-ethmoidal fissure with possibly a discharge discernible in the olfactory fissure and on the pharyngeal wall, or we may see the discharge coming from the sphenoid ostium either with or without the pharyngoscope. A temperature of 99.5° to 101° F. is usual in this infection. Should the secretion be present on the pharyngeal wall its color quickly changes from that seen in the postnasal space to a dark yellow or greenish nature. It becomes very tenacious and scab formation results with the typical cacosmic odor.

Ocular Symptoms.—Beside the symptom of pressure pain back of the eye, sudden or gradual unilateral or bilateral blindness may occur due to compression of the optic nerve in the optic foramen or by perineuritis or toxemia.

Olfactory Disturbances.—These are similar to ethmoidal involvement and due to the mucous membrane in the olfactory fissure and that covering the septal side of the middle turbinate and septum being congested and covered with pus thus olfaction is diminished or lost entirely.

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A CONSIDERATION OF THE INDICATIONS FOR REMOVAL OF THE FAUCIAL AND PHARYNGEAL TONSILS

IN thinking of the indications for the removal of tonsillar tissue of the throat, it is essential that we take into consideration the physiologic importance of these structures as well as the menace to health from pathologic conditions. Many theories have been advanced as to their function, the majority of them being at present discarded. They undoubtedly belong to the hematopoietic organs. The germinating follicles which first appear in the tonsillar structure just before birth are an active source of lymphoid cells which pass from the tonsillar parenchyma out into the efferent lymphatics in the trabeculae. In the normal active tonsil these lymphatics can be seen at all times packed with lymphoid cells. The origin of the germinating follicle is somewhat in doubt. Probably the majority of anatomists believe that they are mesodermic but there is considerable evidence pointing to an epithelial origin. There is no doubt but that in the histogenesis of the tonsil invaginations of the epithelium, which later forms crypts, take place before the formation of the tonsillar parenchyma.

The possibility of an endocrine function of the tonsil has never been substantiated nor do they furnish any secretion that can be regarded as protective against infections of the upper respiratory tract.

It is, however, possible that a certain amount of general immunity to bacterial invasion is brought about by the reaction of the body to absorbed toxic products elaborated by bacteria in the crypts. This has never been definitely established but

the possibility is great enough to make it an important consideration when the question of tonsil removal comes up.

Therefore, I believe that, at least in early childhood, the normal tonsil structures, while not essential to the maintenance of life, have a certain amount of importance in the welfare of the individual. This is further evidenced by the clinical fact that the early removal of faucial and pharyngeal tonsils is frequently followed in the course of the next few years by what might be looked upon as a compensatory hypertrophy of other tonsillar tissue in the throat.

On the other side of the question we must recognize that the tonsils are more liable to bacterial invasion than any other portion of the nose and throat. Further, the toxic products of bacteria and sometimes the bacteria themselves may pass through the cryptal epithelium without local disease, and that on the whole they are more apt to be a source of focal infection than any other part of the upper respiratory tract.

While there have probably been many more deaths following tonsil operations than have been reported and certainly many more alarming complications, the surgical risk of tonsillectomy is not sufficient to contraindicate the operation when there is a sufficient pathologic condition to make their removal advisable. However, I am strongly of the opinion that promiscuous operating on normal tonsils as a prophylactic measure or for other reasons should be utterly condemned.

With the understanding that there must be some reason for the justification of operative interference, let us consider some of the clinical conditions which are indications for operation.

Acute Upper Respiratory Infections.—Recent statistics show that, after a lapse of a number of years, acute rhinitis, laryngitis, tracheitis and bronchitis, are actually more frequent in individuals who have had their tonsils removed than in those who have not been operated upon. However, there are certain cases in which the infection seems to start in the pharyngeal tonsil and another group in which hypertrophy of the pharyngeal tonsil interferes with nasal drainage. In these cases the removal of the pharyngeal tonsil is of course indicated but I do not believe that the removal of the faucial tonsils is ever justified as a prophylactic measure for the prevention of recurrent infection of the respiratory tract.

Tonsillitis.—Recurrent attacks of tonsillitis or peritonsillar abscess present an absolute indication for tonsillectomy. Although the tonsil rapidly recovers from an acute infection it has been demonstrated by histologic examination that where the tonsil structure has been subjected to one or more attacks of acute infection there is very apt to be chronic pathologic changes in the tonsil structure and any attack of acute tonsillitis may give rise to serious complications.

Cervical Adenitis.—It is probable that in about 80 per cent of the cases of infections involving the deep lymphatic glands of the neck, the source of the infection is in the faucial or pharyngeal tonsils. Therefore, recurrent acute cervical adenopathy or the persistence of a chronic enlargement of the glands of the neck constitutes an important factor in the operative indications. It must be remembered, however, that infections can take place through the lingual tonsil, the lymphoid follicles of the pharynx, and the teeth, but in the latter case the submaxillary lymph nodes are primarily involved. It is not uncommon to see acute cervical adenitis develop after thorough removal of the faucial and pharyngeal tonsils especially where a compensatory hypertrophy of the lymphoid tissue of the pharynx has followed the tonsil operation.

In tuberculous cervical adenitis the faucial and pharyngeal tonsils are even more liable to be the course of infection and it is probable that in such cases the tonsils if examined will often show histologic evidences of tuberculosis. I might say here that primary tuberculosis of the tonsil can be demonstrated by histologic examination as occurring in almost 4 per cent of tonsils removed in the ordinary routine, but can seldom if ever be diagnosed clinically.

The removal of the tonsils in cases of tuberculosis is a much more serious proposition than when this disease does not exist. The operation is absolutely contraindicated if there is an active pulmonary lesion. Under some circumstances it might be permissible in the quiescent stage but should never be done under a general anesthetic. If there is no pulmonary lesion and except for the pathology in the cervical lymph nodes the child is in good general condition one might be justified in removing the tonsils, thus hoping to shut off further infection to the lymph nodes.

It must be remembered, however, that the tonsillar structure itself is very resistant to the progress of the tuberculous disease and that in many cases the tonsillar tubercle will become spontaneously healed. Personally, I prefer to treat the tonsils in these cases with the electric cautery, either removing a portion of them with the cautery snare or opening up the crypts rather extensively with the cautery knife. Coagulation may also be judiciously used.

Hypertrophy.—Whether or not the term “hypertrophy” can be properly applied to the tonsillar tissue of the throat is a mooted question. It is certainly true that one individual may have tonsils that are much larger than another without this enlargement constituting a pathologic condition. Yet I have seen many children whose tonsils increased greatly in size following a general infection such as the exanthemata of childhood, particularly measles. When these enlarged tonsils are examined histologically they present an almost normal picture except that the germinating follicles are apt to be very large, which enlargement may be looked upon as a response to the call for an increased number of leukocytes, hence a pathologic condition. Further, it is to be remembered that in children with large tonsils and adenoids who have had them removed early in childhood life there is apt to occur an increase in size of the lymphoid tissue of the posterior pharyngeal wall and lateral pharyngeal folds. This is essentially a true hypertrophy. We must believe then that while true hypertrophy of the tonsil tissue may and does occur, all large tonsils cannot be considered pathologic.

However, no matter what the cause of the enlarged size of the tonsils and adenoids, the clinical problem as to the treatment is essentially the same. Both faucial and pharyngeal tonsils may, because of their size, actually cause mechanical obstruction though this is more true of the pharyngeal tonsil than the faucial, and we frequently have to operate for this reason alone. Because the pharyngeal tonsil is more often a menace to health solely on account of its size than is the faucial tonsil, it is a perfectly justifiable operation to remove only the pharyngeal tonsil. This applies especially to young children, that is, under five years of age. In fact I frequently prefer doing the comparatively simple removal of the pharyngeal ton-

sil in young children though realizing that the faucial tonsils may have to be taken out later on. In following this procedure I believe there is less danger of a subsequent hypertrophy of the lymphoid tissue of the pharynx. Of course in patients who have been suffering from repeated attacks of tonsillitis or present some other positive indications for tonsillectomy we must remove the faucial tonsils as well as the adenoid even under five years of age.

Ear Complications.—Recurrent acute attacks of otitis media constitute an almost positive indication for operative removal of the pharyngeal tonsil, especially if there is any enlargement. Likewise, in cases of subacute otorrhea, whether a mastoid operation has been done or not, an investigation of the nasopharynx is called for and if any amount of adenoid tissue has been found it should be removed. I do not believe that the faucial tonsils are often responsible for acute ear infections except where there has been an acute infection of the tonsil itself.

Conductive deafness, especially in children, demands a careful examination of the nasopharynx and also of the faucial tonsils. It is not uncommon for the pharyngeal tonsil, by its actual size, to produce more or less obstruction of the eustachian tube mouth. On the other hand, a small and unobstructive pharyngeal tonsil probably has little etiologic significance unless it becomes repeatedly infected, which fact can only be determined by clinical observation. An enlarged embedded faucial tonsil may also interfere with the eustachian tube aeration probably both by dampening the action of the tensor palati muscle and by actual encroachment on the mouth of the tube by pushing the upper surface of the palate upward. In considering all these factors it is easily understandable that any ear infection constitutes an important element in the operative indications of tonsillectomy and adenoidectomy.

At times a tonsillectomy is necessary in cases of diphtheria carriers. Of course the operation should never be done as long as the patient shows any toxic symptoms but the organisms may be carried around for months in the depths of the tonsillar crypts, and the removal of the tonsils is often followed by immediate disappearance.

Focal Infection.—The relation of the tonsillar tissue to

systemic disease is not only of great interest to the laryngologist but it has been recognized as an important clinical phenomena by practically every type of practitioner—the internist, the orthopedist, the ophthalmologist, and others of the ilk. The multitude of diseases that have been accredited to tonsillar infection is so great that there would scarcely be room in this article to enumerate them. Further, it is probable that in many of these instances the guilt of the tonsil has supposedly been proved by the benefit following upon its removal. While in many of these cases the tonsils are responsible for the condition we must remember that there is such a thing as coincidence. I remember one child whose pediatrician vehemently urged tonsillectomy which operation was arranged for but had to be put off on account of an acute upper respiratory infection. Six months later the parents brought the child back for operation which I refused to do because the child had entirely recovered from its previous complaint, put on 15 pounds in weight, and was as healthy a youngster as one would care to see. However, it is perfectly true that the tonsillar structures are the most vulnerable portion of the throat to bacterial invasion and constitute a most important etiologic factor in cases of focal infection.

The possibility of systemic reactions from disease in the tonsils is pointedly portrayed in acute suppurative tonsillitis. There is no doubt of the responsibility of the tonsils in these cases. In subacute and chronic infections their responsibility is not so manifest and the determination of the guilt of the tonsils frequently requires considerable clinical judgment.

At this point I want to state that in my opinion there is no criterion obtainable either from history or from clinical examination that will enable us to pass absolute judgment as to the responsibility of the tonsils in any given case of focal infection. Of course certain factors and phenomena may be present that more or less indicate tonsil responsibility.

A careful history which should have for its object not only the number of attacks of tonsillitis, quinsy, or other local inflammations but also the relation of tonsillitis to the beginning of the general systemic condition, has more weight in a proper estimation of the tonsil responsibility than does any local appearance of the tonsil itself.

Probably next in importance is the presence or absence of adenopathy of the cervical lymph nodes. These may either be chronically enlarged and palpable at the time of examination, or there may be a history of recurrent cervical adenitis. Either of these features are important in estimating the possibility of the absorption of toxic products through the tonsils, yet we must remember that infections starting in the lymphatic tissue of the posterior pharyngeal wall and other neighboring areas may also give rise to the adenitis of these glands.

Examination of the tonsils themselves of course gives suggestive data but by no means conclusive. On the whole, a large tonsil will probably cause more systemic reaction than a small one because there is a greater area for absorption, but the large, prominent, or pedunculated tonsil with open crypt mouths is less liable to retain septic foci than is an embedded tonsil with small orifices to the crypts.

The presence of cryptal débris is usually looked upon by the clinician as of considerable significance but I feel that its importance is considerably overestimated. The accumulation of epithelial débris, the so-called "cheesy" plugs, in the crypts of the tonsil is not evidence of pathology. In a crypt with a small mouth the retention of desquamated epithelium is frequently found in a tonsil that appears otherwise perfectly normal histologically. If, however, this material becomes infected by a pathogenic organism, we find a large number of polynuclear cells passing through the epithelium liquefying the cholesteatomatous mass so that instead of squeezing a firm, cheesy substance from the tonsil by pressure, more or less liquid and perhaps foul-smelling material is obtained. This may have the appearance of pure pus and theoretically indicates inflammatory reaction of the tonsil parenchyma. However, I have frequently seen individuals without the slightest evidence of local or general malady showing considerable liquid exudate. Given, however, a case of focal infection, the finding of any considerable amount of pus in the crypts at least increases the possibility of tonsillar infection.

The presence of calculi in the tonsillar crypts would suggest a chronic irritation, but again enormous calculi are sometimes found without any local irritation being present at all.

To my way of thinking a much more significant finding is

the small enclosed abscesses, some of them as large as a pea, others appearing simply as small pinhead-sized whitish areas under the epithelium. It is reasonable to suppose that where one of these abscesses is recognized there may be more unrecognizable in the deeper structures of the tonsils. Toxic products are much more easily absorbed from these enclosed abscesses than from the open draining crypt, but again I have frequently seen them without systemic symptoms. However, the most striking results that I have had following a tonsillectomy for focal infection are in those cases in which such abscesses have been found during the operation, or on examination of the tonsil after its removal.

I differ from some of my confrères in the significance of the congestion of the anterior pillar of the fauces. I have never been able to prove to myself that it is of any significance whatsoever, feeling that the variation in the color of the anterior pillar is due more to the size of the palatoglossal muscle than it is to any reflection of tonsillar congestion.

Hyperkeratosis of the tonsil is in itself an innocuous condition though the keratotic plugs may sometimes act as a culture medium for pathogenic organisms. The majority of these patients, however, do not have systemic reactions and the condition should be considered solely on its local manifestations. As it usually involves not only the faucial but also the lingual tonsil and all of the lymphatic tissues of the pharynx, tonsillectomy does not by any means eradicate the condition, though I have obtained some very beautiful pathologic material by this method.

From the amount of literature that has been written on the subject one would naturally suppose that carefully taken cultures from the crypts of the tonsil would give us a good index to judge the guilt of the tonsil, and quite a number of investigators have asserted that the quantity of organisms found in a given tonsil is equally important with the type.

For a number of years I took careful cultures from the crypts of the tonsils of every private patient who came for an opinion as to the possibility of the tonsils being responsible for their focal infection, and for a while I thought that the presence of hemolytic streptococcus or *Streptococcus viridans* was a distinct indication for operative removal of the tonsils. How-

ever, as time went on and I had opportunity to observe the results in these cases I concluded that the bacterial examination of the cryptal contents even when made by a very careful technic did not furnish any conclusive data. I still feel, however, that in some cases this examination should be done, but worth while information can only be obtained by following out a careful technic. By ordinary swab cultures it is impossible to avoid surface contamination.

I suggest the following method. After anesthetizing the surface of the tonsil, so that the tongue can be kept depressed while the culture is being made, the surface of the tonsil is sterilized with tincture of iodine and then a sterile platinum loop or similar small applicator is introduced deep into the crypt of the tonsil. From this, one culture tube is inoculated and a second culture is then taken from the surface. If we find an organism growing from the material taken from the crypt, while none grow from the surface culture, we have good reason to suppose that we are getting bacteria from the crypt itself.

Statistics published in the last few years concerning the frequency of various general infections as occurring in persons who have had their tonsils and adenoids removed, as opposed to those who have not undergone operation, seem to indicate that certain types of infection are more liable to originate in the tonsils than are others and it might be well to give a brief synopsis of these statistical findings.

Chorea—primary attacks apparently occur as frequently in operated children as in nonoperated children.

Endocarditis—primary attacks are less frequent in operated children than in nonoperated but the removal of the tonsils does not by any means prevent the primary occurrence of this disease or secondary exacerbations.

Rheumatism—subacute arthritis occurs less frequently in operated cases than in the nonoperated cases. In chronic arthritic conditions statistics are not conclusive.

Infectious ear lesions are less in operated cases.

Respiratory infections—rhinitis, laryngitis, tracheitis and bronchitis are more frequent in operated cases than in those who have not been operated on.

General malaise due to mild toxemia is frequently caused

by tonsillar infection but statistics are not available as to the ratio of occurrence between operated and nonoperated cases and the same applies to a number of other conditions such as prostatitis, toxic goiter, nephritis and other kidney conditions, various eye lesions of toxic origin, toxic labyrinthitis, and perhaps certain types of gastro-intestinal disorders.

Considering the subject of focal infection as a whole and the relation of the tonsillar tissue to it, I believe our attitude should be somewhat as follows: If a patient is suffering from a malady that is incapacitating or severe enough to warrant a tonsil operation for its relief, and if this malady in the opinion of the internist, or other physician, is focal infective in character, and if all other sources have been eliminated, the tonsils should be removed no matter what their history or appearance is, except in those cases where one by inspection sees such small normal bits of tonsillar tissue in the fauces that it is inconceivable that they should be a source of infection. When tonsil infection is possible but not probable, it is better to eradicate all other possible gateways, such as the teeth, perhaps the sinuses, the gallbladder, before proceeding with the tonsillectomy. We can never tell our patients that the operation is surely going to relieve them of the source of their infection, but as a result of the study of the history and of our clinical examination, we can justly say that we think there is perhaps a 25 or 50 per cent possibility that the tonsils are responsible.

In closing let me call your attention to the fact that tonsillectomy is not, except in very rare instances, an emergency operation and that a time should be chosen for the operation which will best safeguard the patient from accidents and complications.

It should of course never be done during the presence of an acute infection of the upper respiratory tract and it is wisest to wait at least three weeks after the last symptoms of the infection have disappeared. The same thing holds true of acute infections of the tonsil itself except in those rare instances, and I have seen one such case, where the swelling of the tonsils is so great as to cause dyspnea and in this case the tonsils were not only removed but tracheotomy also had to be performed.

The operation should never be done following closely after any of the infectious diseases of childhood and this is especially

true of measles. I have made it a rule not to operate on any case that has had measles for at least six months after the attack.

In spite of some opinions to the contrary, tonsillectomy should not be done in patients with pulmonary tuberculosis.

In potentially allergic patients the operation should be postponed to a time of year when the air is practically pollen free. There is a distinct possibility for parenteral inoculations to take place through the tonsil wound and I have seen a number of children with hay fever whose symptoms started following a summer tonsil operation.

In endocarditis the operation should be postponed in the large majority of cases until the acute symptoms have subsided though a mild valvular lesion I do not consider a contraindication if the operation is necessary.

Patients with pyelitis or albuminuria should be studied carefully before tonsil operation is undertaken, though in some cases the operation may have to be done in the presence of albuminuria as nephritic lesions may be caused and kept active by septic foci in the tonsils.

Finally, in selecting a time for the operation, the physical welfare of the patient is our first consideration and we should not permit ourselves to do the operation at an unfavorable time because of parental or social urgency.

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THE CONSERVATIVE TREATMENT OF SEPTIC
TONSILS

BOTH the physician and the alert layman are today increasingly cognizant of the vast importance of the faucial tonsils in respect to public health.

Education and compulsory medical examination of all children in the public schools, with particular bearing on the senses of sight and hearing, and inspection of the ears, noses and throats of the pupils, has done much to make the layman health conscious and more responsive to medical advice. Recognition has been granted as to the responsibility of septic tonsils in the causation of many disease conditions and complications.

The diseased tonsil, even the hypertrophied but seemingly nondiseased one, carrying as it almost invariably does, virulent streptococci, must be seriously considered, and certainly when causing systemic symptoms, should be enucleated. The prevalence of tonsil infection is universal and infectious in the highest degree. Of more than 6,000,000 children attending the government schools in England, from 8 to 10 per cent had enlarged, diseased tonsils.

The function of the tonsils is but little understood; many observers believe them of no value, some that they act as immunizing agents. Adam compares the tonsils to a sponge which, so to speak, is wrung out when the muscles of deglutition contract, the material so wrung out passing into the intestinal tract, and when the muscles relax, the sponge is ready to absorb further supplies of whatever toxic material may be in the mouth.

Complications of tonsil infection may occur anywhere in the body, but are most common in the ears, the paranasal

sinuses, and in such diseases as arthritis, neuritis, dermatitis, myocardial and endocardial complications, cholecystitis, appendicitis, nephritis and encephalitis. Frequently their influence is observed in peribronchitis, pneumonitis, lung abscesses, oophoritis, puerperal fever and many others. Mock has noted that those with chronic tonsil infections are more liable to infections of the hands and feet than those with normal tonsils or when tonsils have been removed. Hall states in regard to appendicitis, that in an observed series of more than three hundred cases he had not seen an appendix removed, nor had he removed one, in a case where tonsils had been removed in childhood.

It is generally conceded that the severer types of throat infections are comparatively rare in tonsillectomized cases, and that diphtheria and scarlet fever, when occurring in these operated cases, are usually extremely mild. Zilkowsky reported over a thousand cases of scarlet fever in which only twenty-three had been operated for removal of tonsils and these unsuccessfully. Rhoads and Dick even go so far as to say that if any case contracts either scarlet fever or diphtheria, the tonsils or faucial lymphoid tissues have not been removed.

Recognition of the prevalence of tonsil infection and its rôle in the causation of general diseased conditions, exists in its present advanced light today only after the constant antagonism of skepticism has grudgingly yielded to modern medical experience. As late as 1906, Ewart of "St. Georges" Hospital, London, was regarded by his colleagues as a mentally unbalanced individual, because he advocated the removal of septic foci, such as defective teeth and infected tonsils.

A far cry it is from the "massacre of the tonsils" of John MacKenzie, to the voice of experience by Dan McKenzie, who says "I can remember the generation of children before adenoids were known. I remember the discharging ears and the deafness; I remember the dirty noses and the thick excoriated upper lips; I remember the scrofulous glands in the neck; I remember the vacant stupid faces; I remember the dacryocystitis, weeping pus; my companions I have seen dying in middle life from heart disease contracted in childhood after tonsillitis. Then I turn and look at the young men and

maidens of today, clean of health and stature, and I see the transformation of a race through the influence of a simple operation." Furthermore, McKenzie doubts the value of statistics used to disprove this point, and asks whether the figures are reliable; whether in fact, in those cases where focal disease has developed after tonsillectomy, we have any statistics to prove that the tonsils were completely removed, or whether the adenoids were not alone removed in some cases, and whether a recurrence of this lymphoid tissue was excluded by competent examination.

E. J. G. Beardsley recently remarked, "For over thirty years I have been impressed with the harm done by allowing foci of infection to remain in the body. The greatest evil is that caused by infected tonsils. I have a great admiration for the progressive physicians of the nose and throat specialty, who have accomplished more for public health than any other group, possibly with the exception of those who have taught and advocated a safe water and milk supply.

"The removal of infected tonsils and teeth in children renders them much more safe against infective diseases and makes them a much better health risk. Much inferior surgical work, however, has been performed in this particular branch. Many men are attempting operations for which they have neither proper training nor skill. This should be corrected by proper sentiment within the profession."

If we accept the premise of acceptance by the body medical of the rôle of the infected or septic tonsil as a definite contributing factor in the causation of many disease conditions, what methods shall we adopt for the treatment or elimination of such foci?

After rather scanty suggestions for local applications in the treatment of each of the many classifications of tonsil inflammation or infection, the average textbook goes into lengthy, many paged, descriptions in step by step detail, of many types of individual's operative procedures, from finger dissections to enucleations in numerous varieties, from the simplest technic to the most complicated. The method of choice must ultimately lie with the individual surgeon.

In addition, it matters little what technic or armamentarium is used, provided the end-result is complete eradication of

every vestige of infected tissue without mutilation. Complete removal seems to have few, if any, harmful effects. Gardner reports that it has been the custom in Abyssinia for time out of mind, following a pandemic of septic tonsillitis, to remove the tonsils of all children in infancy by means of fingernail dissection and the application of a horsehair loop, the latter tied around the semi-enucleated mass, and in a short time the pedicle is severed and the tonsil usually swallowed by the infant. He cites the Abyssinians as a stalwart race, noted for centuries for their strength and warlike characteristics.

But even the most radical exponent of surgical removal of septic tonsils must admit that conservatism in many instances is mandatory, and that discretion must compel us to conduct the treatment of these cases with nonoperative procedures. Foolhardy indeed would we be to attempt surgical intervention in patients suffering from acute systemic disease such as pneumonia, typhoid, acute cardiorenal disease, tuberculosis, uncontrolled lues and the like. Hemophilia and various blood dyscrasias necessitate serious consideration before considering operation, as well as abnormalities of blood supply, particularly of the internal carotid artery. Hemangiomas too, though rare, usually contraindicate surgery; the premenstrual and menstrual period may be less seriously regarded. Acute inflammatory disease of the tonsil, from any cause, compels respect and caution. Chronic arthritis with joint changes should make us less hopeful of good results from surgery, but not necessarily discourage it. Cases suffering with sarcoma, Hodgkin's disease, carcinoma and the like are seldom considered safe for surgical procedures unless recognized early.

Granting the necessity for conservatism in the treatment of many patients with diseased tonsils, let me outline and discuss the usual accepted methods of treatment in these cases. The first essential is attention to oral hygiene. Since the tonsils cannot be removed, every effort must be given to effect elimination of other sources of infection which tend to perpetuate the tonsil inflammation. Bad teeth, suppurative ears and paranasal sinusitis must be actively treated when possible. It is surprising how much benefit is evidenced in tonsils when the effects of a course of dental hygiene procedures have time to manifest themselves. Gargles and sprays so universally used

by the patient are of some help, but are not nearly so effective as lavage given by the physician with large quantities of solution to penetrate thoroughly and empty the crypts of the tonsil of their septic concretions. Better still is that ingenious suction spray apparatus by which we are enabled to spray cleansing antiseptic solutions into the crypts, as suction keeps them open to facilitate their emptying of their toxic contents.

The effect of cold quartz light and ultraviolet seems to be beneficial in many instances, by reason of its causing a localized leukocytosis.

Radium has been used to cause atrophy of the tonsil with, at times, disappearance of the disease for the time at least. It does not remove the tonsil itself. Operation is the only means of removing a tonsil completely. Radium does increase fibrous tissue, decreases lymphatic tissue, causes disappearance of the follicles and a decrease in lymphocytes. Its use has become less and less frequent excepting in the treatment of malignant growths and hemangiomata.

Roentgen rays act upon the tonsil in the same manner as the gamma rays of radium. They differ in that they must be applied externally through the tissues of the neck before reaching the tonsils. Only a few years ago many enthusiastic proponents of this technic, particularly among the family of roentgenologists, were about ready to predict the doom of tonsil surgery.

At that time I was treating a patient for whom I advised tonsillectomy, despite knowing him to be an intimate friend of a very prominent roentgenologist who was then advocating x-ray therapy for infected tonsils, almost to the utter exclusion of surgical proceedings. As I had anticipated, the patient, knowing about x-ray treatment, asked to consult his friend about his personal problem. I knew his physician friend was inherently honest, so I was not at all surprised when my patient returned to me to report that after examination his friend said,

"Because of our friendship for many years, I shall not treat you with x-ray. I suggest that you have them removed surgically."

Naturally, since then I have been loath to employ x-ray in cases other than those suspected of malignancy.

Lastly, it is necessary to mention the treatment of chronically infected tonsils by electrosurgery. Electrosurgery, coagulation or desiccation is by no means intended to replace well-established surgical enucleation except in selected cases. Unfortunately the method generally has fallen into disrepute by reason of incomplete results in the hands of men untrained in any type of tonsil surgery, who having purchased an expensive piece of apparatus, feel that they must make it pay for itself.

The promiscuous, uncontrolled, and untrained use of this method in the hands of many physicians has filled the clinics of hospitals with incompleated cases who, having spent all their available funds for an unsuccessful removal of their tonsils, must now ask for free treatment for relief or further operative extirpation.

Properly used by those trained in its use, it fills a welcome niche in our armamentarium. By painstaking care, frequent observation and follow-up, it is possible, I believe, to eliminate all tonsil tissue in many instances, but it should be used only in those cases in which removal by other surgical means is entirely contraindicated.

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EARLY ATTENTION TO THE LARYNX IN TUBERCULOUS PATIENTS

EARLY recognition and early treatment of pulmonary tuberculosis is one of the most important factors in the successful outcome of this disease. Indeed, the reduction of this malady has been brought about not only by early recognition of existing disease, but also by prophylactic measures in those susceptible to the disease and those exposed to it.

Excepting in those sanatoria, or tuberculosis clinics where examination of the nose and throat is a routine procedure in all cases of pulmonary tuberculosis, invasion of the larynx is usually well under way before it is recognized, and treatment is rarely begun until long after the onset of this complication.

C. L. Minor,¹ a pulmonary specialist says: "The result of this failure to recognize that the larynx is an essential part of the respiratory system, which must be studied in every complete pulmonary examination, has been to delay disastrously the early diagnosis of this disease in very many cases, so that too often it is not found in those stages when it is most curable, but only discovered when pronounced symptoms, such as hoarseness, dysphagia, aphonia, etc., force it upon the doctor's attention.

"When these symptoms . . . appear it is so far advanced as to offer little prospect of successful treatment."

It is generally believed that tuberculosis of the larynx is a complication of the pulmonary disease and rarely if ever a primary lesion, and that the mode of invasion is by implantation of the bacillus from the mucosal surface in most cases and to a less degree by means of the blood stream. Some writers state that the tubercle bacillus may reach the submucosa

through intact epithelium. What I believe is this, that prior to the lodging of the tubercle bacillus in the submucosa, there has been a denudation of some of the epithelium as a result of inflammation affording a foothold to the bacillus in the submucosa and then regeneration of the epithelium over the implanted organism, resulting in a histologic tubercle.

If the larynx is properly cared for at this time, in addition to treatment of the pulmonary lesion, the tubercle may become healed. If however the larynx is under par, the tubercle may develop, caseation occur and ulceration result. This ulceration becomes the prey of pyogenic invasion resulting in still further spread of the lesion; however, not all the ulcers in a tuberculous larynx are tuberculous. Many of them are pyogenic ulcers. This has been demonstrated by microscopic examination of sections from ulcers of tuberculous larynges obtained at autopsies.

Tuberculous lesions are not always confined to the submucosa, but tend to spread inward to the deeper structures resulting in perichondritis and chondritis. When this occurs pseudo-edema results, especially when the epiglottis or the arytenoid cartilages are invaded. The epiglottis may become completely destroyed and the arytenoid cartilages may be sloughed out.

Symptoms.—Unfortunately, the early lesions of the larynx are practically symptomless. Some of the cough in pulmonary tuberculosis may be due directly to the irritated larynx but rarely does this suggest itself to the physician.

Voice changes are so gradual that the attending physician and even the patient is frequently unaware of the fact that he is hoarse until the lesion is well advanced.

Too often slight intermittent hoarseness and sensations of dryness are attributed to a passing attack of simple laryngitis during the course of the pulmonary disease and ignored. Nothing is done until the hoarseness becomes constant or the patient complains of distress upon swallowing. The laryngologist is then expected to affect a cure or to relieve the dysphagia. By this time it is dangerously late and the hope of cure or relief is remote.

Symptoms of tuberculosis of the larynx occur comparatively late in the disease. Even small lesions on the vocal

cords themselves, especially near the vocal angle produce voice alterations so slight that they remain undetected until the lesion has attained such size that approximation of the cords is interfered with. Lesions on the posterior wall also remain symptomless for a comparatively long time. Ventricular band lesions rarely produce symptoms other than a sense of irritation. Epiglottic and arytenoid lesions notably pseudo-edema present the most urgent and painful symptoms, *c. g.*, dysphagia (odynphagia). Usually these lesions occur after the intralaryngeal lesions, but sometimes they may produce the first symptoms in a larynx in which the lesion is far advanced.

It is true that cure or at least arrest of laryngeal tuberculosis has occurred in all stages of the disease, but usually as the disease of the larynx progresses the probability of cure diminishes. If a cure is effected in the late stages it is only at the expense of much hard work and skill on the part of the laryngologist and internist with the cooperation of the patient himself that it is brought about. In the very early stages of the laryngeal disease the task is much easier and the results much more encouraging.

As the laryngeal lesion progresses an increased tax is placed upon the nutrition and comfort of the patient. An otherwise hopeful lung lesion becomes less and less favorable. As the lung lesion progresses general resistance to the disease is decreased and the laryngeal lesion becomes less manageable thus resulting in a vicious circle.

The physician attending a pulmonary tuberculosis case should not be lulled into a sense of security because the pulmonary disease is steadily improving. The improving lung lesion is no indication that the larynx is free from disease or that existing laryngeal disease is improving. Many times have I had patients referred to me with the statement that the pulmonary disease was quiet, but that laryngeal symptoms appeared more or less suddenly. Examination usually revealed advanced laryngeal tuberculosis. The explanation is that although symptoms had only recently appeared, disease of the larynx had been present for some time. This would have been discovered had the patient received proper early and periodic laryngeal examinations from the beginning of the pulmonary disease.

Mortality statistics in the United States show that in the past quarter century pulmonary tuberculosis has moved back from third place to seventh place. Tuberculosis specialists state that pulmonary tuberculosis is decreasing steadily and this is due to a determined effort to conquer the disease in its earliest stages and to prevent its occurrence in those susceptible or exposed to it. The same methods in considering laryngeal tuberculosis, I feel, would accomplish equally brilliant results.

Most pulmonary tuberculosis cases are victims of upper respiratory infections. Indeed it is unusual to see a normal nose and throat in a tuberculosis patient. The seriousness of the pulmonary lesion seems to obscure the gravity of the upper respiratory infections in the minds of the average physician.

All cases of pulmonary tuberculosis should be under the care of both the internist and the laryngologist from the very beginning of the pulmonary disease. If the patient's nose and throat is in a healthy state these examinations could be made at monthly or longer intervals. If, however, there is existing upper respiratory infection, these should receive appropriate treatment until cleared up.

Sinus infection should be cleared up. Necessary steps should be taken to insure proper ventilation and drainage of the nose. Diseased tonsils should be removed. All of this can be done if the pulmonary disease is latent or in the earliest stages; however, all decisions in regards to surgery should be made jointly by the internist and laryngologist and never by the laryngologist alone.

In the more advanced stages of the pulmonary disease surgery may be contraindicated and the treatment confined to non-surgical methods.

If proper attention be paid to the nontuberculous infections of the upper respiratory tract there is no doubt that many cases of active tuberculous laryngitis would be prevented. Unnecessary unproductive cough due to simple inflammation of the larynx and trachea can be relieved by local treatment, which is possible only in the hands of the laryngologist.

Vocal rest, the most important treatment in tuberculous laryngitis, can be used to great advantage as a preventive

method in the laryngeal inflammations, which occur in the course of pulmonary tuberculosis.

Education of the patient with regards to his larynx is of greatest value before laryngeal lesions appear. It is more difficult after the patient develops unmistakable laryngeal symptoms.

Modern methods of dealing with pulmonary tuberculosis, which are highly successful, are greatly handicapped in the presence of laryngeal tuberculosis and frequently nullified in many cases. Cooperation of the laryngologist is of tremendous value to the internist if sought early enough.

Summary.—The average case of laryngeal tuberculosis is first seen by the laryngologist at a dangerously late stage of the disease.

The general practitioner should be educated to the point where he will seek the assistance of the laryngologist immediately upon the diagnosis of pulmonary tuberculosis.

The larynx of the tuberculous patient should be prepared to withstand the invasion of the tubercle bacillus by removing all causes of irritations of the larynx.

Laryngeal symptoms are evidence of existing disease and frequently are absent until the disease is in an advanced stage.

Periodic laryngeal examinations are indicated in all cases of tuberculosis at the very beginning of the pulmonary disease.

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CLINIC OF DR. DOUGLAS MACFARLAN

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PREVENTION AND TREATMENT OF DEAFNESS

Prevention.—In studying the subject "Prevention of Deafness," some thought must be given to the various causes of this handicap, and a conception must be had of the relative proportion of the different types of deafness. Prevention will conveniently be considered separately for each type.

Congenital Deafness.—Statistics (so often accepted as accurate merely because they are called statistics) are most misleading when one considers the causes of deafness. Pick up the survey made for the Rockefeller Foundation by Dr. Richardson's committee, or the annual reports of any of the schools, and you might believe that 50 per cent of the 16,500 children in the 183 institutions for the deaf are congenitally deaf. But, stop awhile, to think of the indefinite or blank histories in many of these cases. There is no accurate record obtainable as to the possibility of birth injuries, a mother may even have forgotten whether instruments were used or not. The story is just as indefinite as to the child's history between its birth-date and the coming of language, age two. We wonder if there were earaches and ear discharges, a spell of fever that might have meant a meningeal attack; fits, spasms or convulsions that might have been something more than erupting teeth. As one of the workers in the Richardson survey, I was struck by the finding of a very high percentage of residual hearing in cases called "born-deaf." This item, unfortunately, was overlooked in the report, but the fact remains that it is hard to fully reconcile the presence of considerable residual hearing with congenital deafness. Wherever there is a possibility of a doubt, I believe in giving the child the benefit of it. if for no other reason than to keep hope alive

that something can be done to use the residual hearing. Some deaf children can be profitably kept out of institutions and taught in day schools for the deaf, or in more normal home environments (parents have something besides the hopeless attitude that they have had in the past when told that their child was born deaf).

This discussion would seem far afield from the subject of prevention, yet the use of the residual hearing in these cases will forestall the complete attention deafness that comes where hearing is not reached. It will often prevent the development of the deaf voice, and it will speed up the acquirement of language, an essential feature of the problem.

True, there is congenital deafness, plenty of it, too much of it. It is seen in inbred, isolated communities and sects. It is seen in the marriage of degenerated stock. It is seen in consanguinity and most often in the inheritance from marriage with a deafened person or in marriage between the deaf. As a prophylaxis, this could be controlled to a considerable extent.

Inherited deafness does not always appear at birth. Many investigators recognize a factor of inheritance in otosclerosis, and yet this deafness rarely appears before adolescence. Numerous cases seem to warn us that this disease is often "touched-off" by a catarrhal attack in the ear. Perhaps there is some reason to believe this; perhaps the catarrh merely causes a more noticeable increment in a beginning slight deafness. In either event, we know that we do not want a catarrhal deafness superimposed upon and adding to any other type of deafness; and with prophylaxis we hope to accomplish most against head catarrhs.

Meningitic Deafness.—It is the blackest disaster that strikes hearing. Deafness is nearly always sudden and complete. There is no residual hearing and even though language has been acquired (the child of three, four, or older) it may soon be lost and the deaf-voice develops. The best advice is to get the child under a competent teacher of the deaf *as soon as possible*.

Syphilitic Deafness.—Syphilitic deafness, once thought to be common, on the contrary is found to be rare. There is no higher incidence of positive Wassermanns in school for

the deaf, than among normal children. Ergo, congenital syphilitic deafness is rare.

With adults, deafness is not a common accompaniment of the disease. The onset may be sudden or slow, often one ear is affected at a time. The deafness may be partial or complete. Tinnitus and dizziness are usually present. The pathology is leptomeningeal or central. All known treatments are indifferently successful, either as to improving the hearing or as to arresting the deafness.

Otosclerosis.—Otosclerosis, the enigma of deafness, diagnosed only with certainty by postmortem, cause and relief unknown. What more of an obstacle could be presented, except cancer? With otosclerosis, however, the victim has time to:

1. Learn lip-reading while there is still residual hearing to help.
2. Adjust psychologically and economically, so as to avoid the certain unhappiness that comes when these items are overlooked.
3. Hearing-aids may hold off the time of silent isolation. (The prospect of the otosclerotic is not necessarily overdis-
mal, the deafness may stay stationary for long periods. In the beginning, the deafness is not necessarily profound.)
4. Any tendency to superimposed catarrhal deafness must be conscientiously combated by the otologist if he can but get the cooperation of the patient. Catarrh seems to aggravate otosclerosis.

Chronic Progressive Deafness.—The older otologists still use this classification; to many it serves as a useful pigeon-hole in which to put otosclerosis, to others, it serves to cover "ideopathic" deafness of the nerve type, symmetrical in both ears, gradual in onset, and as certain in its progression as the rise in taxes. In this class can surely be placed such deafness as comes as a result of chronic toxic influences. These cases are seen in those who use too often and too thoughtlessly such proprietaries as contain the salicylates, quinine, certain arsenicals and possibly the barbiturates. Many of these drugs are concealed behind innocent trade names; they are advertised through every serviceable means of reaching the public; and are even helped on their way by their careless prescrip-

tion by the doctor. Careful experimental work, such as that done by A. G. Pohlman, leaves no doubt as to their danger to hearing. (Aspirin is probably the worst offender.)

Other chronic toxic influences on hearing are suggested in certain cases of focal infections, bad teeth, infected tonsils, chronic gallbladder catarrh, colitis and chronic constipation. Many "rheumatic" cases exhibit this type of deafness in low degree.¹

Senile Deafness.—Ere life's race is run, there is little wonder that some damage has not occurred to the most delicate of sense organs. Sclerosis alone should have appeared. Catarrhs of the tract have come from time to time, and each has left its effect. The noise of this noisy world, should alone account for some of this old-age deafness. Or, perhaps, the old man has just gotten tired of listening. Attention is a factor in many cases of senile deafness.

Occupational Deafness.—Occupational deafness is a recognized entity in certain trades; the prophylaxis is obvious.

Physical Violence to the Ear.—Physical violence to the ear must not be overlooked as a cause of deafness (*e. g.*, the child whose ears are boxed, and the sportsman whose companion shoots before he thinks). Here, irreparable damage may be done, not merely in rupturing a drum, but actually in dislocating the organ of Corti off the basement membrane (Lurie).

Catarrhal Deafness.—By far the most important cause of all degrees of deafness, of deafness beginning at any age after birth, is catarrh of the upper respiratory tract. The following categorical statements abbreviate the topic.

Catarrhal deafness of 9 to 12 per cent is usually handicapping. Such degree of deafness is often overlooked unless tested by audiometry.

Deafness may insidiously develop from: (*a*) chronic nasal catarrh; (*b*) chronic sinus infection; (*c*) deflected septum with its sequelae; (*d*) postnasal drip; (*e*) adenoid overgrowth; (*f*) tubal catarrh; (*g*) chronically retracted drums; (*h*) middle

¹ Tobacco is believed by some to affect hearing, but, if so, should there not be more deafness? Likewise, alcohol, a case in point was the deafened alcoholic whose hearing improved on his abstaining. However, he went back to his bad habits, because "the things he heard were so much worse than the things he drank."

ear catarrh. Some of these conditions are primary, some secondary.

(i) Infectious fevers, especially scarlet, diphtheria, and measles, may bring on catarrhal deafness, *with or without the appearance of an acute ear*. (j) The chronically discharging ear means the gradual progression of deafness from an inconspicuous amount to a permanent handicap. Nutrition, general hygiene, and general good care contrast with their opposites in the incidence of persistent "colds" and catarrhs.

Treatment.—The author feels that for the most part the subject of treatment has been covered while considering prevention in the foregoing pages (except for catarrhal deafness). In many instances, the treatment is obvious or else the deafness beyond treatment (congenital deafness, postmeningeal deafness). For otosclerosis, there is no known nor proved remedy.¹

If relief of a situation is to be considered treatment in these incurable types of deafness, there must be stressed with the most serious insistence *the value of lip-reading and of hearing aids*. As long as usable hearing remains it must be kept in service. Psychological adjustment, too, is essential therapeutics for the deaf. Never leave the deafened man without a little hope. This does not mean dishonesty, it merely means standing back of him, giving him the right sort of courage, sympathy and interest. Without this, he will surely turn to despair or to the charlatan who will catch him by a promise.

The Treatment of Head Catarrh.—The treatment of head catarrh offers the best encouragement to do something for the catarrhally deaf patient. It should arrest his deafness. If nerve deafness is also present, it should remove an added threat to his hearing. In brief, the treatments for catarrh can be listed in a general way, their application falling in line as the "punishment fits the crime."

1. Stop the chronically discharging ear even if you have to do a simple mastoid. But, first try all the classical methods, then ionization. If these fail, operate.

2. Correct chronic nasal catarrh, chronic sinusitis, post-nasal drip, adenoids and tubal obstruction. Remember general

¹ I do, however, like to deceive myself into thinking that the prolonged and conscientious use of the iodides tends to arrest the progress of otosclerosis.

hygiene, try vaccines and tampons if you will. Do not omit to wipe the tube mouths clean with gauze when doing an adenectomy. Get the postnasal turgescence down, and restore nasal respiration with its aeration. Play with bouginage of the tubes if you believe in it (I do not), but use politzerization judiciously as an aid. Remove diseased tonsils on their own culpability, but do not promise by so doing to improve hearing.

3. Test the hearing, preferably by phonograph audiometer, at every session. Inexpensive audiometers, motor-driven, with an electric pick-up, are now available. Keep careful and full records. Try to keep the patient conscientious and try to sustain your own interest in an ultimate object. If costs deter the patient, budget your services on an annual basis, and let the patient come as often as he can come. Promise nothing but a conscientious, sustained, and intelligent effort on your part. Then, if the patient cooperates, you will get results.¹

¹ For the child without speech or language, where a determination of hearing is desired, the author recommends the conditioned reflex as the best and only way of testing for residual hearing.

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THE DIAGNOSIS AND TREATMENT OF MUCOUS NASAL
POLYPS, WITH A CONSIDERATION OF THE ALLER-
GIC FACTOR

Introduction.—Since we first offered, in 1933, convincing evidence of the primary rôle which allergy plays in the etiology of mucous nasal polyps, this concept has gained recognition among both allergists and otolaryngologists. It has, however, as yet not found its way into textbooks on general pathology, nor has it been adequately stressed in general medical teaching. For the most part, the literature on the subject is found only in special journals and a few texts in the special fields of allergy and otolaryngology. It, therefore, seemed desirable in this communication, to call the attention of general practitioners and internists to the importance of a recognition of the underlying sensitivity in the causation and perpetuation of mucous nasal polyps and to outline certain practical points of procedure which these cases call for.

Space does not permit a detailed restatement of the proofs that allergy is a constant factor in the etiology of mucous nasal polyps: these details the reader will find in our previous communications.^{1, 2} In brief, the chief points are these: The incidence of mucous nasal polyps is strikingly high in allergic diseases of the respiratory tract, particularly in those allergic states which continue throughout the year, asthma and perennial allergic rhinitis. The incidence of nasal mucous polyps is extremely low in patients whose presenting symptoms are those of nonallergic diseases, even though these diseases entail a high

incidence of paranasal sinus infection, as in bronchiectasis or lung abscess. This is sharply at variance with the older concept that infection is in some way the underlying cause of such polyp formation. A critical study of the occasional patients with mucous nasal polyps and without an obvious major complaint of an allergic disease nevertheless shows that these individuals are commonly of an allergic heredity, that they themselves often have other manifestations of allergy and, what is most important, they are sensitive usually to inhaled substances in their environment and that the avoidance of these substances can prevent the recurrence of polyp formation. Particularly convincing is the fact that avoidance of, or desensitization with allergens yields clinical results far superior to the old routine of surgical removal alone, with its distressingly frequent recurrences of the polyps.

The practical problems which face the physician in these cases include: (1) the finding of the nasal polyps, with an exact determination of their site, size and extent; (2) the establishment of the precise nature of the polyps, that is, whether they be true mucous polyps or another form of polypoid tumor; (3) a complete diagnosis covering all abnormalities in the nose and sinuses; (4) a complete survey from the allergic standpoint as to the possible etiologic sensitizing substances; (5) a choice of treatment procedures in the light of the above findings.

The Clinical Examination of the Nose.—It may not be unduly presumptuous to call the attention of the general practitioner to some of the general principles of nasal examination as well as certain pitfalls, which may beset the path of the not too-skilled examiner. While it is true that direct inspection through a nasal speculum will discover most polyps, it must be remembered that small polyps in the deeper recesses of the nose will escape detection unless the nose is examined with a nasopharyngoscope. This necessitates a careful and prolonged application of any of the accepted shrinking agents on tampons or applicators in order that a maximum field of vision is provided. Examination with a nasopharyngoscope must, therefore, be a routine procedure. The presence of polyps should always be suspected when the nasal mucosa shows extreme pallor and extensive edema. The examiner, however, must be on his guard not to mistake a pallid edematous middle

turbinate for a mucous polyp, an error that is very easy to commit.

While recognition of a well-developed pedunculated polyp is simple, detection of the earlier polypoid alterations is at times difficult. Moreover, cocaine, adrenalin and similar shrinking agents frequently so alter the turbinal mucosa that the resulting pallor and nodulation may simulate the appearance of early polypoid change. This may necessitate reexamination after the effect of the shrinking agent has partly or largely worn off.

We have been impressed by the frequency with which mucous polyps occur within the paranasal sinuses.¹ While 30 per cent of asthmatics are found to have polyps on intranasal inspection, it is probably true that an even higher percentage would be found to have polyps in the sinuses if their interior could be inspected. Thus of 50 asthmatic patients that were subjected to the Caldwell-Luc operation, 34 showed polyps on intranasal inspection; all 34 were found to have antral polyps as well, and an additional 10 had antral polyps in the absence of intranasal polyps. The finding of intranasal polyps or even extreme pallor and edema of the nasal mucosa, with or without early polypoid change, should lead the examiner to suspect the possibility of polyps in the sinuses. α -Ray examination of the sinuses should therefore routinely be carried out in addition to the clinical examination in all these cases. It is to be remembered that the transillumination of the frontal and maxillary sinuses may show fairly good light transmission even though the sinuses be the site of extensive polypoid change.

Exact notation should be made of the sites from which the polyps spring, particularly in relation to the sinus ostia. This further directs suspicion to the sinuses in question. It has been our experience that intranasal polyps tend to spring from the junction of the respiratory and olfactory mucosa. While the olfactory membrane is largely limited to a small area on the septum and a corresponding area on the superior turbinate, dissection of fresh preparations demonstrates the presence of olfactory fibrils in the tissue of the middle turbinates. There are also small islands of olfactory mucosa at some distance from the principal olfactory area.

The Establishment of the Diagnosis: Mucous Polyp.—

The certain diagnosis of mucous polyp can be made only upon

histological examination. The microscopic examination of the tissue removed should therefore be a routine procedure. While it is true that the great majority of polypoid lesions encountered in the nose are true mucous polyps, there are other types of polypoid change which can at times closely simulate mucous polyps but which have an entirely different etiology. Neurogenic tumors grossly are very similar to mucous polyps. Moreover, since they arise from the filaments of the olfactory nerve, they occur in practically the same localities as do mucous polyps. Yet they are a form of malignant growth and as such require suitable treatment.

It would seem appropriate at this point to give a brief classification of the types of polyps which may occur in the nose.

1. *Mucous polyps* (myxoid fibromas) may be simple or multiple. They are usually but not exclusively pedunculated. They are smooth, pale, translucent, often glassy in appearance. Their color varies from a translucent white or gray to bright yellow or reddish yellow and, if they have been long subjected to dust or irritants, may show marked discoloration. They are characteristically soft and jelly-like and unless palpated may be mistaken for mucus. When punctured, their serum content readily escapes, leaving an insignificant tag. Microscopically, they show hypertrophy and edema of the tissue from which the polyp has arisen, but although arising from mucous membrane, show no mucous glands or only their scanty remains. The epithelium varies from a thin layer of columnar cells to a thick, many-celled layer of stratified columnar epithelium. The older the polyps, the less likely are there to be ciliated cells. The bulk of the polyp consists of an edematous tunica propria with loosely disposed areolar fibers enmeshing a considerable quantity of albuminous fluid, at times suggesting cyst formation. The cellular constituents are relatively inconspicuous and include migratory lymphocytes, round cells, plasma cells, mononuclear cells and eosinophiles. The presence of eosinophiles depends primarily, as we have shown,² upon the time which has elapsed since there has been pronounced exposure to a sensitizing substance. Thus we have found eosinophiles present in large numbers in a polyp removed from a patient during the hay fever season, whereas polyps removed from the same patient only a short time after

the pollen season was over showed practically no eosinophiles. This is an important point, since it has been claimed by some, that the absence of eosinophiles in a mucous polyp is evidence against the presence of allergy in that patient.

2. *Mixed polypoid hyperplasia*, as Kaufmann³ points out, is in structure essentially similar to the mucosa but is more markedly cellular. Its appearance is red or grayish-red. Histologically, it may show glandular hyperplasia with dense vascular formations as described by Hopmann,⁴ or there may be angiomatous, highly vascular lesions of obvious characteristics. This group is comparatively rare.

3. *Papillary hypertrophy* or *mulberry polyp* is differentiated primarily by its papillary form. Appearing in the posterior end of the inferior turbinate, the mass consists of hyperplasia of the turbinal mucosa in which cystic degeneration of the glands and dilatation of the vessels have occurred. Its papillary structure, its usually red color and its firm consistency readily differentiate the mulberry from the mucous polyp. These are also comparatively rare.

4. *Malignant forms*, all of them comparatively rare, include carcinomatous, sarcomatous and neurogenic polyps. The importance of early and accurate histological diagnosis in this group is obvious.

Investigation of the Allergic Factor.—The diagnosis of mucous polyps having been established, it now becomes necessary to study the patient from the standpoint of allergy. This entails first of all a thorough-going history from the standpoint of sensitivity. The patient is questioned in regard to other manifestations of hypersensitiveness, notably asthma, hay fever, allergic rhinitis with excessive sneezing or with profuse, watery nasal discharge or with recurrent blockage of the nose by mucosal swelling; eczema, urticaria, recognized idiosyncrasy to specific foods or drugs, and migraine. The family history should also be carefully investigated from the standpoint of these allergic phenomena. In almost every instance the examiner will get affirmative answers to some of these questions.

The patient should next be subjected to thorough-going skin tests with an extensive list of foods, pollens, animal emanations, specific contact substances, such as kapok, cotton-

seed, orris root, and with house dust. It is particularly desirable that he be tested with dusts to which he is exposed in his home or his occupation. In our experience by far the greatest number of patients with mucous polyps are found sensitive to inhaled substances, particularly house dust and such animal epidermal substances and specific dusts to which they are perennially and intimately exposed. It must be stressed, however, that the range of substances tested must be large and all-inclusive, since it is the rule that patients are found sensitive to a number of substances rather than to only one or two.

General Examination.—It would appear uncalled for to emphasize to internists the need for considering the patient as a whole and not merely as a case of nasal polyps. Nevertheless, there are several points in this connection which experience has shown to be worthy of stress. Just as it is true that the allergic individual is usually sensitive to numerous substances, so does he usually present more than one clinical manifestation of such sensitivity. This may be fairly obvious in case of other respiratory allergic conditions, such as an allergic bronchitis or asthma, or may be found only on more careful study when such allergic symptoms occur in the digestive tract, the urinary tract or elsewhere. The allergic patient is of course subject to the same ills as his nonallergic brother and the recognition and treatment of these must therefore be a part of the clinician's procedure. Rather more frequent in the allergic than in others, in our experience, has been the finding of gastric anacidity. The exact relationship of gastric anacidity to allergy is unknown. It is our feeling, however, that gastric anacidity may play a part in the development of sensitization by way of the digestive tract in allergics who happen to have gastric anacidity.⁵ The recognition of the anacidity is important, since its treatment is efficacious in the management of these patients.

It must also be remembered that the patient with nasal polyps may present himself primarily to the internist, not because of polyps, but because of another allergic disease. The patient may consider his nasal difficulties of minor importance and may be quite ignorant of the presence of polyps. This is particularly true in the patient whose nasal symptoms began in childhood, and to which the patient has become so accus-

tomed that he does not realize that his nasal condition is abnormal. Thus, for example, it is routine procedure in our allergy clinic to examine the nose and sinuses of all patients, whether they have primarily nasal or other complaints. Not infrequently we have discovered nasal polyps and other evidences of nasal allergy in patients sent to us primarily because of an allergic eczema. Careful nasal examination as above outlined should therefore be a routine procedure in all allergic individuals.

It is also worth emphasizing at this point that patients with nasal polyps far more frequently first present themselves to the general practitioner than to the rhinologist. The clinician should therefore be prepared to make an adequate examination of the nose and sinuses.

Treatment.—To understand the principles of treatment of mucous polyps, one must keep in mind the main points in the natural history of these lesions:

1. Mucous polyps are the result of long-continued allergic edema in tissues in which such edema, because of anatomic peculiarities, can gradually produce the polypoid tumor.

2. If the cause, that is, the substance or substances to which the patient is sensitive, is removed sufficiently early from the patient's environment, the lesions in the mucosa are reversible and early polypoid change or even moderate-sized polyps may regress and disappear.

3. If the polyps are large and have been long present, the pathologic change is no longer reversible and the lesions will persist even though the cause be removed.

4. If mucous polyps are operatively removed, but nothing is done about the underlying sensitivity, then the continued action of the allergens or sensitizing substances will inevitably lead to the formation of new polyps.

In the light of these facts the following general rules of treatment procedure are obviously warranted:

If, as is usually the case, the polyps are large and offer considerable obstruction to breathing and the natural drainage of the sinuses, then their removal is imperative. The first important point in this connection is the selection of the time at which the polypectomy is to be done. When an operation is performed on the upper respiratory tract of an allergic in-

dividual during a pollen season, we have pointed out that there is a definite danger that the allergic patient may become sensitive to the pollens prevalent at the time of his operation. If at all possible, therefore, polyps should be removed before active pollination begins (in Philadelphia, for example, about the middle of April), or after active pollination has ended in the fall (in this region about the first of October). The next point to emphasize is that the polypectomy must be thorough-going and complete. This may necessitate a 2-stage operation with an intervening submucous resection, removal of large septal spurs or possibly a partial turbinectomy, in order to gain a satisfactory approach to the deeper recesses of the nasal chambers. Particular care should be paid to the ethmoidal regions. It is a common mistake to remove a few larger polyps, and to leave behind clusters of small polypoid masses that effectively block ethmoidal drainage.

This leads up to the next important point: the adequate management of sinuses, notably antra and ethmoids, which are so commonly involved in these patients. It is futile to remove nasal polyps and to leave untouched antra and ethmoidal sinuses filled with polyps and only too often secondarily infected. In correcting the sinus involvements it cannot be too much emphasized that in the long run thorough-going "radical" sinus surgery is at the same time the most effective and the most conservative treatment. It is, therefore, usually indicated that the rhinologist perform radical ethmoid exenteration and, in the case of the antra, the Caldwell-Luc operation.

If the patient presents only early polypoid change, operation may prove unnecessary. But whether an operation is performed or not, careful and thorough attention to the allergic factor is always and constantly in order. This entails, first of all, complete avoidance, whenever possible, of the substances to which the patient is sensitive. Thus if the patient is sensitive to feathers, there should be no bedding or upholstery containing feathers in his home. Yet only too often the feather-sensitive patient changes only his own pillows while his marital consort in the same room, or even the same bed, continues to use a feather pillow. If the patient is sensitive to orris root, no one in the household should use cosmetics containing orris root. One of our patients obtained relief only after he supplied

the secretarial force in his office with nonallergic cosmetics. The diet should be strictly limited to those foods which give negative skin reactions. The patient's bedroom floor should be bare and the room should be devoid of upholstery or unnecessary hangings. There should be no pets in the patient's household. The first axiom of the treatment of allergy is that the avoidance of allergens gives the best clinical result.

If complete avoidance of allergens is impossible, then active attempts must be made to lessen the patient's sensitivity by appropriate injection treatment. Thus if he is pollen-sensitive he should be thoroughly treated perennially or pre-seasonally and coseasonally each year with the appropriate pollen extract. The commonest unavoidable allergen in our experience with polyp cases is house dust. In the case of house dust sensitivity, complete avoidance is rarely possible. It is therefore usually necessary to treat these patients with an extract prepared preferably from their own house dust. Similarly it may be necessary to treat patients with extracts of orris root, feathers, animal epidermal substances and the like when complete avoidance of these substances is for one reason or another impossible. This has rather frequently been the case when an individual is sensitive to substances to which he is exposed in the course of his occupation. Not infrequently in such cases, the search for the offending substance, when limited to his house environment, proves fruitless until the dusts of his occupational environment are studied. Since under these circumstances it frequently is not feasible for the patient to change his occupation, attempts must be made to treat him with extracts prepared from the dusts to which he is exposed at his work.

In all patients, particularly those who have been subjected to nasal surgery, there must be a careful follow-up with re-examination of the nose at regular intervals. This includes, first of all, careful postoperative treatment. Only too often good nasal surgery is nullified by inadequate postoperative care, permitting the formation of dense adhesions and synchia. In the second place, it will lead to the detection, first, of old polyps that may have been overlooked at the first operation and, later, will discover the possible formation of new polyps. The latter case is evidence that either known allergens

have not been adequately avoided, or that desensitization treatment has not been adequately carried out, or that further active allergens remain undiscovered. In the latter instance, the case should be thoroughly reviewed and every effort made to discover the unknown causes.

Appropriate treatment should, of course, be directed against any other abnormality which the patient may possess. If his stomach does not produce sufficient hydrochloric acid, then hydrochloric acid should be administered regularly with his meals. A mistake which the allergist not infrequently commits is to restrict the patient's diet sharply on the basis of skin test findings and so to inflict upon the patient a diet which may in various ways be inadequate. Care should therefore be taken to see that, within its limitations, the diet is nevertheless properly balanced and adequate as to mineral and vitamin content. To achieve this, it may be necessary to supplement the diet by the administration of the proper minerals, notably calcium, and vitamins.

Since secondary infection is often present in the sinuses of these patients, and since they are not infrequently more vulnerable to respiratory tract infections than the normal, an important part of the treatment of such patients is commonly the administration of a suitable vaccine. At times this may well be an autogenous vaccine, frequently, however, a stock vaccine proves helpful. In the administration of such vaccine treatment these points are worthy of emphasis: Dosage should begin at a lower level than is usually the case in vaccine therapy. Thus the initial dose should preferably not exceed 10 million organisms. The increase of the dosage should be gradual, avoiding as much as possible either severe local or any general reaction. The interval between doses should be at least four days and preferably a week. When higher doses are reached, the interval should be even further prolonged. The vaccine administration should be continued over many months.

The whole situation may be summed up in these words: Complete and accurate diagnosis of the anatomical lesions in nose and sinuses; recognition of all the substances to which the patient is sensitive; thorough correction of the anatomical defects by proper surgical procedure; thorough handling of the allergic factors involved; systematic recheck of all factors to

guard against relapse; the treatment of the whole patient, not merely of his nose.

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SYSTEMIC DISEASES CAUSING INFLAMMATION IN THE EAR, NOSE AND THROAT AND THE LOCAL MANAGEMENT OF THESE CONDITIONS

THE purpose of this clinic is to present as clearly as possible the acute and chronic inflammatory reactions noted in the upper respiratory tract as complications of a selected group of general systemic diseases and suggest their most logical treatment. The clinical treatment of this assignment would at first appear to be a simple matter, but on further analysis the scope of the subject is great and there is such variation in type, stages and acuity of systemic background as well as in the topical picture, that it almost becomes a textbook effort to cover the field adequately. For example, some 25 major diseases are definitely causal in affections of the ear. As some pathologic irregularity in the upper respiratory tract might be found in every substantial hematologic variation, its ramifications could scarcely be computed. If the statement be true that a careful blood culture taken each hour of the twenty-four would, at one or another period, find organisms even in a normal healthy individual, blood stream reaction in the ear, nose and throat is unavoidable and the systemic etiology is a definite one.

Resisting the temptation to digress into pattern of textbook dissertation, the aim of this clinic should be simply to cull from impressions of experience the most likely types of upper respiratory infection, complicating certain systemic diseases, make sure of sufficient repetition for an adequate guarantee of identity, and then post a few valuable signboards that "those who run may read."

The busy practitioner has been taught in the medical school that 60 or 70 per cent of cases in his early practice will have predominant upper respiratory symptoms and in his

equipment he is prepared to meet this situation. These troubles do not all originate here, and the blending of systemic and local is etiologically confusing.

This earnest man, alone with his patient, simply wants to know what local manifestations this particular systemic disease is likely to present, or conversely to what systemic background do the certain local disturbances in the ear, nose and throat point. As an acute inflammation, unchecked, should tend to become chronic, the chronicity in itself would not seem to thwart its value in diagnosis. In fact, inflammatory maturity in certain conditions, for example syphilis, tuberculosis and malignant disease of the larynx, strengthen confirmation in diagnosis, so the stage and acuity latitude would aid the scope of this study.

It remains then to select a few representative diseases, study their local symptoms and prescribe an adequate treatment. Perhaps pneumonia, typhoid fever, syphilis, tuberculosis, scarlet and rheumatic fever form a sufficiently formidable sextette of representative diseases for initial attack. These are selected because their own diagnosis is distinctive, etiology, symptoms and stages fairly definite, and routes for extension of complication fairly clear. Their order in placement is based more on popularity, than either alphabet or severity.

A second group is presented for study as far as time permits, a sextette rather of systemic conditions than distinct entities. Perhaps these conditions might be considered as bearing somewhat the same relation to diseases of independent title as the technician in the department bears to his professor. May we name these: (1) allergy, (2) agranulocytosis, (3) influenza, (4) diabetes, (5) diphtheria, (6) streptococcic infection. In the main, their study is a more generalized one and their own diagnosis less simple.

In this study, matters of mere statistics will as far as possible be minimized, and upper respiratory manifestations will often be found quite identical in different diseases.

Pneumonia.—The most adequate pneumonia studies have been made in hospital wards, and the incidence of aural and sinus complications in pneumonia have been particularly well covered and published in pediatric studies. In resistant cases of pneumonia, one should perhaps first study the oropharynx

with its postnasal discharge, the spheno-ethmoid areas in the nose and the middle ear. The spheno-ethmoid area may be studied even in fairly young children with a small nasopharyngoscope or antrascopes and early tympanic examination is indicated in pneumonia because its advent is so insidious and often quite painless. Published statistics in the younger group of cases have indicated about 30 per cent of aural complications in pneumonia, with a rate doubly high in infants under two years. Sinusitis appears from research studies to be always present in some degree in pneumonia. Under the same category may we emphasize the fact that the middle ear, by proper definition, includes the eustachian tube, tympanic cavity and mastoid. When the tympanum is suppuratively involved, the adjacent mastoid (antrum) area is also infected and while one author credits only about 16 per cent with mastoiditis in 116 cases of clinical otitis media in pneumonia, we must realize that many initial mastoid infections and especially those in pneumonia subside spontaneously, and we suspect that in definite suppurative otitis media there will probably be 100 per cent involvement of the mastoid antrum. Postmortem post-tympanic and mastoid culture studies have also borne this out.

It has been conclusively demonstrated by good authority that the treatment in acute sinusitis should be nonsurgical and the pneumonia complication not only fails to present an exception but its development of systemic immunity adds emphasis to nonintervention. In the suppurative stages drainage is of paramount importance. This may be obtained through judicious use of the various shrinking agents of the cocaine (2 to 10 per cent) and ephedrine ($\frac{1}{4}$ to 3 per cent) type and the use of nontraumatic suction by the combination glass bulbs or the small-calibred soft rubber catheter and suction apparatus. The possibilities of retarding or destroying normal ciliary activity should be considered.

In otitis media of pneumonia, so often of the serous, so-called "catarrhal" type, prone to spontaneous absorption, and often automatically relieved by the relief from toxic symptoms in the disease itself, one should proceed slowly in opening the middle ear. Not every red ear drum requires incision. Do not mistake a myringitis or a collection of serous fluid, for a septic middle ear. During examination, the clarity of the lines of the

ossicles in the tympanic membrane should be helpful in diagnosis. In a fully developed bulging tympanic membrane these ossicular lines disappear. If the short process and handle of malleus are still seen, it is presumptive evidence that there is little intratympanic pressure present. As the more dangerous of pneumonic infections seem to show least tendency to spontaneous discharge and drainage, it is perhaps wise when in doubt to incise—the first incision should be an adequate one, with a generous circling in posterosuperior and postero-inferior quadrants. No subsequent incision will be equally effective. In some cases discharge may be slight but at least you have contributed toward thwarting deeper mastoid infec-



Fig. 170.—Tympanic membrane with position of injected vessels.

tion. In the middle ear with mastoid complication, organisms probably follow the frequency rule—streptococcus, hemolytic and nonhemolytic most predominant, pneumococcus, especially Type III, second, and mixed staphylococcus third. So in this day we must bow to our newer therapeutic sulfanilamide ally and give it a prior chance. Investigations have not yet rendered a clear verdict as to its bacterial indication, but it has proved most abortive in its effect and one can afford to await its aid in thwarting further complications.

Transfusion of blood and other serological measures will aid the little patient's resistance and while the entire effectiveness of sulfanilamide in both streptococcic and pneumococcic

infection is still in experimental stage, we are inclined to believe it has already superseded even the immunized and pool serums.

Mastoiditis, definitely established, lateral sinus thrombosis and meningeal involvement are fields of specialist's care and do not belong in the limitations of this clinic.

The most interesting pneumonic complications coming under observation have been toxic deafness, one in pneumonia and one in typhoid which were profound, bilateral, and quick in onset. These were evidently basal meningeal in type and were seen in convalescent stages of basic disease. Medication had to be consistent with the systemic care. Iodides in the form of Donovan's solution was permitted in one case. Both cases recovered. We suspect their recovery would have been hastened had we then been acquainted with sulfanilamide.

IN PNEUMONIA, KEEP WATCH OF SINUS AND MIDDLE EAR DISEASE!

Typhoid Fever.—As in pneumonia, the intercurrent sinus and middle ear infections predominate the complication tally. In typhoid fever the otolaryngologist is impressed with what might be termed the atonic toxicity or nonresistance of the patient. While acute and suppurative otitis media, acute rhinitis and sinusitis, are frequently present, there still is a pervasive sort of atrophic rhinopharyngitis with dull, injected membranes, sticky almost immovable tenacious mucous collections; the nose and throat carry the impression of systemic nonresistance and depletion, ready ulcerations which are sluggish in healing, rhagades, rather edematous hyperpharynx, ribbons and bridges of tenacious nasal secretion. In the sluggish glandular picture of typhoid one should be on the watch for the ulcerations and even low-grade abscess formation. This care should include anterior septal membrane, surface of oropharynx, epiglottis and intrinsic laryngeal structures, alveolar margins and internal buccal surfaces. This laryngeal involvement might even progress to perichondritis and necrosis of the cartilages.

In this state of affairs, laryngeal stenosis with all its gravity would be a natural sequel. Consequently, just as daily tympanic examinations are indicated in pneumonia, so in the

presence of hoarseness, whether from weakness or laryngeal pathology, the larynx should be examined every two or three days. When chronic changes are recognized, routine treatment, antiseptics, inhalations or other medications should be advised, but no cauterizing agents used in acute or simple chronic involvement. In the use of inhalants it is well to remember that an ill-managed inhalation may be more irritative and harmful than its entire absence. Deep sluggish abscesses should be appropriately and stimulatingly treated. The toxic involvement of auditory pathways and cochlea are much to be dreaded. The nonperforative seropurulent involvement of the middle ear in typhoid usually disappears after the run of the disease is over, but often remains as adhesive processes in the middle ear. These are contributory to the disturbances in hearing which seem to be caused both by labyrinthine changes and action of typhoid infection on the auditory nerve or center. In addition to passage of septic material or extension of inflammation through the eustachian tube from the nasopharynx it has been asserted that emboli in the middle ear from endocarditis or distant pus collection may be contributory. Tympanic perforations when present are posterior and larger at the beginning than ordinary perforations. The prognosis in middle ear infection of typhoid is relatively more favorable. As in pneumonia, the carefully guarded convalescence from the original typhoid disease will very likely be attended with an upper respiratory convalescence as well.

IN TYPHOID, OBSERVE THE SLUGGISH, NONRESISTANT MUCOUS SURFACE; KEEP CLEAN AND GUARD ULCERATIVE AREAS!

Syphilis.—Perhaps more in syphilis than in any other systemic disease does its stage count, in its upper respiratory complement. It is interesting to note the low percentage of luetic cases appearing in a mass study of laryngeal cases—in Logan Turner's group only 6 per cent in about 2400 laryngeal infections were specific.

In congenital syphilis, the initial picture is that of an acute laryngeal catarrh, later becoming hyperplastic, often with papilloma-like excrescences. The picture is one of diffuse hyperplastic infiltration. The primary stage chancre may

rarely appear about the lip region of the lower palate and pillars, or epiglottis. It shares the characteristics and course as when on the genitalia. Mucous patches of the second stage occur in the oropharynx, epiglottis and laryngeal areas.

Fig. 171.



Fig. 172.



Fig. 173.

Fig. 171.—Syphilis of the larynx. Inflammatory reaction involves principally the anterior half of the larynx.

Fig. 172.—Tuberculosis of the larynx. Inflammatory reaction involves principally the arytenoids and posterior half of the larynx.

Fig. 173.—Carcinoma of the larynx. This illustration is included as an aid in the differentiation of carcinoma from the two other common laryngeal diseases shown on this page.

Specific nasopharyngeal involvement may spread to the ear via the eustachian tube, and sometimes from specific ulceration and condylomatous hyperplasia, produces a lower stricture; the middle ear and cochlear sequelae are what one would ex-

pect. Syphilis of the middle ear is difficult to diagnose. Some mild specific infections occur and disappear without recognition. The rapidity of tympanic membrane destruction and the lowered bone conduction might give specific suspicion. A Wassermann test is, of course, imperative but if positive would not isolate the ear in its decision. The routine treatment here and in the nasopharynx is antiseptic and palliative with greater dependence upon systemic medication. In nearly all these sinus blocks, mild shrinking measures, with some ephedrine-like agents, combined with mercurial or other antiseptic, would be appropriate.

Nothing but systemic antiluetic medication can be done about the drop in hearing. Such is due either to direct extension from middle ear infection, by circulatory route or through parasymphilitic thickening, diminishing the single avenue of blood supply to the labyrinth coming directly from the basilar. This is apt to attend the sort of "neurorecidiv" shock on the administration of neoarsphenamine. If the disease is under prompt and early treatment, much of the deafness may automatically clear.

In third stage of syphilis one should look for these tertiary infiltrations, due to small cell proliferation.

The characteristic gumma may more often occur in nasal septum, epiglottic folds, posterior laryngeal wall or even below. Subsequent ulcerations and necrosis may produce havoc in the larynx with fixation of one cord and marked general deformity. Syphilitic papillomata may appear more often in posterior commissure, a space rather preempted for tubercular demonstration.

IN SYPHILIS, LOOK FOR SECOND- AND THIRD-STAGE DEMONSTRATIONS IN OROPHARYNX, NASOPHARYNX, MIDDLE EAR AND LARYNX!

Tuberculosis.—Laryngeal tuberculosis is admittedly secondary to pulmonary or bronchial gland tuberculosis. In certain young children up to three or four years of age, tubercular otitis may be primary, and of course in nasopharynx and nose may be of mixed air-borne origin. Tubercular laryngitis and tubercular otitis media are the two more important phases of systemic complication. The laryngeal diagnosis is reasonably

simple. Its arytenoid swelling and inter-arytenoid cauliflower thickening are locationally characteristic and chest evidence and sputum give complementary value. The diagnosis in ear is more than difficult and almost dependent upon granulation tissue necropsy or animal inoculation. It affects the ear as lupus externally or otitis media and mastoiditis. Its onset often follows a coughing blow up the eustachian tube and sense of fullness in the ear with persistent deafness even after the middle ear is seemingly clear. The membrane is thickened, dull and vessels dilated. Often spontaneous in discharge, the single or multiple perforations have advocates.

In our own cases less is observed of pinpoint lesions or presence of actual tubercles. Such have been well pictured in ear microscopic studies of Luscher in Berne. There is difference of opinion as to ossicular destruction which we are inclined, however, to emphasize.

It has been stated that of all cases of chronic suppurative involvement in children, over 15 per cent are tubercular, and we know that any pyogenic involvement favors tubercular progress. Infections in the middle ear may come via eustachian passage, or more rarely by blood and lymph stream. Wood has pointed out that entrance is possible through both pathologic and unbroken epithelium as well as via gland mouths and traumatic abrasions.

The disproportionate continuance of deafness and tinnitus in a quite painless middle ear involvement is most suggestive. Treatment is the general treatment of tuberculosis plus local cleanliness, antisepsis, removal of secretion and in the ear perhaps diathermy and radium.

While radical mastoid surgery has been advised, consensus of opinion would favor conservative, nonoperative interference except in urgency. An interesting epidemic of streptococcic throat infection among tuberculosis patients has been reported.

IN TUBERCULOSIS, WATCH OUT FOR LARYNGEAL CHANGES AND MILD INITIAL MIDDLE EAR INVOLVEMENT WITH PERSISTENT DEAFNESS!

Scarlet Fever.—The entire group of exanthematous diseases might be considered here "en masse" but there are advantages in singling out a single bad actor, study its behavior

and treat accordingly. Scarlet fever so involves the upper respiratory tract that were it not for its profound effects elsewhere, noticeably the kidneys, it might be withdrawn from the systemic list. Its first effect in the upper respiratory tract is in characteristic rhinopharyngitis. This is characterized by a vivid erythema of oropharyngeal mucous membrane, particularly tongue and palate, rather less than in measles. This is succeeded by increased nasal discharge and soon involves the sinuses. In severe cases of sinus involvement, all layers are involved and even necrosis or osteomyelitis may follow. A frequent accompaniment is edema of the larynx. All these symptoms may subside with acquired immunity of the disease though ear, sinus and laryngeal complications may be seriously continued.

Characteristic of scarlet fever otitis media, is the thrombotic type of invasion with its lightning-like involvement of the tympanic area, rapid passage by continuity to the antrum and mastoid, and development of a hemorrhagic rather than a coalescent type of mastoiditis. This does not follow the rather quiet ordinary type of hemolytic or nonhemolytic streptococcic infection. With its other exanthematous leader in middle ear invasion, measles, the question of procedure is often a delicate one. Should this middle ear infection be speedily released and should the mastoid be promptly operated without customary delay for safety walling off for meningeal protection? Even-tual surgery is reasonably sure and much must be left to the judgment of operator and study of patient's condition. Lateral sinus thrombosis and blood stream infection may readily occur, but there are usually advance signals such as septic temperature and local symptoms. It will be noted that the activity of scarlet fever and measles are quite differentiated from the toxic metastasis of infectious parotitis and diphtheria.

The rhinitis, oropharyngitis and laryngeal involvement are not essentially different in scarlatiform and ordinary acute invasion of simple areas. The erythema of palate and strawberry tongue, are principally valuable from a diagnostic point of view. The preliminary antitoxic measures and serology in therapeutics are indicated for local as well as general immunity, ordinary alkaline antiseptic treatment for nose and throat and routine cleansing management of noncomplicated middle ear

involvement. Perhaps more often the simple instillation of 2 to 5 per cent phenol in glycerin is an advisable routine.

The sinus involvement should invite gentle suction but no drastic measures in early stages. Sulfanilamide has not been effective.

Frequent blood examinations including cultures should accompany the urinary examinations in sthenic type of disease. Cure the sinusitis for the carrier's sake, give convalescent serum and finally x-ray treatment. Look out for laryngo-tracheitis.

IN SCARLET FEVER, WATCH OUT FOR OROPHARYNGEAL ERYTHEMA, SLOW-DEVELOPING SINUSITIS, EDEMA OF THE LARYNX, EAR AND KIDNEY COMPLICATIONS, AND GUARD AGAINST CARRIERS.

Fig. 174a.



Fig. 174b.



Fig. 174c.

Fig. 174a.—Typical bulging of the tympanic membrane.
 Fig. 174b.—Intratympanic serous fluid line in middle ear.
 Fig. 174c.—Intratympanic serous fluid line with air bubbles.

Rheumatic Fever.—The question of the systemic acute rheumatic fever versus upper respiratory complications resolves itself really into a discussion of the tonsil infection as a primary focus or secondary occurrence.

The onset of acute rheumatic fever has been found more often to follow an acute streptococcic-like flare-up in the throat. The conventional red injection of throat, particularly palate and pillars, with sharp febrile reaction, often pseudomembranous deposit and culture, and smear demonstration of streptococcic predominance of strains, has been rather convincing as to this relation. After an attack of rheumatic fever the secondary streptococcic type of persistent sore throat convinces one again of the interrelation.

We must put against this the discouraging report before the Academy some years ago, giving statistics of 2200 cases and results before and after tonsillectomy. A recent careful review in Children's Hospital studies of postoperative and unoperated tonsil children by Dr. Rachel Ash at the Mary Drexel Staff Clinical Conference, was likewise illuminating and a bit discouraging to the ardent tonsil operator. As acute articular rheumatism only produces in our observation acute rhinopharyngeal and tympanic reactions, it is fair to devote some study to the lymphoid analysis. Much valuable work by Schenck and others has been done upon the pathology of tonsils and lymphoid lateral and other pharyngeal masses in acute rheumatism. The finding of these definite pathologic areas which to visual diagnosis are represented in the bright red lymphoid patches on the pharynx and the deep almost mulberry injection of anterior pillars and adjacent portions of palate, is convincing. While it appears rather evident that removal of septic tonsils is not going to cure an established septic endocarditis, there are certain tonsil and lymphoid tissue observations which should be helpful. Diagnosis of tonsil sepsis should be confirmed, not by observation of cryptic masses and follicular debris but by producing typical pus from upper poles and certain crypts, on eversion and pressure upon the tonsil by definite redness of anterior pillars before manipulation and similar injection of other lymphoidal masses and the pericryptal margins.

After removal of tonsils the statement is often made that "my throat is no better than before." The answer is that compensatory excess of lymphoid tissue has appeared in the pharynx, especially lateral columns. This is poorly protected by thin covering membrane which easily succumbs to infectious flood coming down the pharyngeal wall in event of acute or chronic sinus attacks. The pharynx lights up and these lymphoid masses are taking the place of former removed tonsils as toxic foci. Either these accessory masses should be removed coincidentally with tonsil removal or they should be removed, cauterized or obliterated by diathermy subsequently.

The reaction after secondary procedure is a "recidiv" proof of its importance. Cultures from tonsils almost invariably show hemolytic and nonhemolytic streptococci and sometimes the *Streptococcus viridans*. The consensus of questionnaire opinion has been in favor of the focal importance of tonsils, greater in some viewpoints, than teeth or sinuses.

RHEUMATIC FEVER—IF THE THROAT SHOWS ACUTE INFECTIVE EVIDENCE AFTER ACUTE RHEUMATIC ONSET, WE AGAIN REITERATE, REMOVE TONSILS AT EARLIEST CONVENIENT TIME.

Allergy.—In reviewing the second sextette suggested, we shall present as it were only "thumb-nail sketches," and bring out certain interesting points. Allergy while not an official systemic disease, is an official systemic condition. Its meaning is abnormal reactivity and it should not be simply relegated to the sinuses, ear or whatever its customary working abode. It includes in its phenomena various hypersensitive forms such as the edema in urticaria, asthma and hay fever, or if in deeper tissues the so-called "angioneurotic" edema, and includes certain types of eczema which in and about the ear canal come under our group of inflammations. Allergy in the internal ear, probably another edema type, may be responsible for certain phases of tinnitus, deafness and vertigo, elements in the Ménière complex. Edema and hyperemia of the respiratory tract comes within our scope. The vasomotor changes in the pale swollen turbinate areas are at least negatively inflammatory. Its diagnosis is already presented by 200 or more valuable surface sensitization tests. Treatment is the immunizing to sensitive agents, careful regulation of offending foods, treat-

ment of nose and throat by the adrenalin, ephedrine, neosynephrin and cocaine shrinking agents to aid drainage. Combined with antiseptic care and in such conditions as eczema, treat on conventional lines, avoiding too much moisture in local treatment, but using various appropriate ointments and powders. We urge against surgery during the allergic state if it can be avoided.

IN ALLERGY, FIND THE SENSITIZING AGENTS AND TREAT ACCORDINGLY!

Agranulocytosis.—This title is selected as representative of the blood dyscrasias and their ulcerative lesions in the mouth and throat. Such dyscrasias, according to Tribble, include aleukemic leukemia, agranulocytosis, mononucleosis, syndrome due to sulfanilamide, leukopenia, noma and Paget's disease. Discussion of agranulocytosis from its hematopoietic origin, the deleterious effects of certain barbiturates such as amidopyrine, and other bone marrow poisons causing faulty maturation of the leukocytes, is not pertinent to this paper. We are, however, vitally interested in its oropharyngeal ulcerations; deep sloughing ulcers with exposure of underlying alveolus, deep in its invasion of pharynx, pillars, and lingual tonsil area. There is often an associated Vincent's infection. Perhaps the treatment may be suggested by review of that accorded in one of the author's cases in association with Dr. FitzHugh: x-ray to long bones, blood transfusions with added neoarsphenamine, and local persistent treatment with perborate background, of topical applications of 25 per cent trichloroacetic acid (tissues previously brushed with 2 per cent cocaine) and followed by a thorough application of 10 per cent neoarsphenamine in glycerin. This patient got well, though fully 75 per cent of cases are fatal and the oral ulcerative tract cleared up with the general trouble, minus a few unimportant molar teeth.

This trouble is under constant study, its character far from full interpretation and therapeutics can still only be a suggestive one.

AGRANULOCYTOSIS—WITH ANY SUSPICION OF THE DISEASE HAVE POLYNUCLEAR LEUKOCYTE COUNT AND AVOID BARBITURATES AND SULFANILAMIDE!

Influenza.—It is the belief of many that influenza is sinus-born and perhaps should be termed a sinusitis rather than a disease entity. Its systemic command, however, is so broad, particularly in epidemics, that it seems rational to consider it here. Its upper respiratory influence seems almost definitely directed to antral disease and middle ear and mastoid involvement. Its inflammatory characteristics in these areas are not unusual but the disease produces a sort of tissue depression, either from patient's personal prostration or general systemic sluggishness. The rhinitis and sinusitis are sluggish to treatment, the middle ear and mastoid are tedious in recovery: cleanliness, mild antiseptic irrigations sometimes sulfanilamide, suction, sinus displacement and irrigation are in order. Saline solution is preferable to most antiseptics for irrigation. Middle ear and mastoid surgery will not show rapid "pick-up" and we believe the necessity for many a radical mastoid operation owes its allegiance to an intractable grippe infection.

INFLUENZA—TREAT THE SINUSES AND THE EAR MAY CLEAR UP RAPIDLY!

Diabetes Mellitus.—Here is a systemic disease without much reference in general story to the upper respiratory tract and yet is carrying a dangerous background for upper respiratory dyscrasias. An otolaryngologist does not like to operate a diabetic patient from a sort of biochemical apprehension. By the same token the patient should be and is susceptible to upper disturbances and diabetes is one of the constitutional dyscrasias which cause acute rhinitis. This rises and falls with the sugar level. Diabetic patients are prone to furunculosis in the ear canal and nasal vestibule as elsewhere on skin surfaces.

Diabetes weakens the tissue resistance to other infections. In a recent diabetic case a marked middle ear and tinnitus of very obstinate character developed, which even refused to yield to specialized tinnitus treatments. This is the first particular case of that sort associated with diabetes, that has presented.

Treatment of both ear and rhinal episodes is conventional. The proper insulin aid will facilitate recovery.

DIABETES MELLITUS—SUSPECT A RHINITIS OF BEING SYSTEMIC ACCOMPANIMENT IN DIABETES!

Diphtheria.—This is a sufficiently constitutional disorder to require the constitutional administration of antitoxin for its

control. Its manifestations are of course local. Its inflammatory picture is the hyperemia, swelling, membrane of fibrous exudate, adherent and bleeding on removal. It must be diagnosed from Vincent's angina, coalescent follicular tonsillitis, mycosis, specific and tubercular ulceration and streptococcic exudate. Its treatment varies from alkaline antiseptics to the mercurial and chlorine solutions, but little progress will be made without regulated antitoxin administration. Diphtheritic laryngitis may require intubation or even insertion of tracheotomy tube and the famous "life-saver" of Mosher is always a valuable traveling companion of the otolaryngologist. In laryngeal diphtheria, antiseptic steam inhalations often with carbolic solution may be indicated; sedative, benzocaine, iodine and carbolic lozenges are of value. Diphtheria may produce a severe rhinitis, where exudate will be found in postnasal and nasal passages and require local antiseptic attention, of course depending upon antitoxin for cure.

DIPHTHERIA—DEPEND UPON LOCAL TREATMENT ONLY FOR LOCAL RELIEF AND COMFORT OF PATIENT!

Streptococcemia.—Systemic streptococcic blood stream infection may come from throat, mastoid and sinus or other focal pocket of streptococcic infection. Its manifestations in the throat are a bright redness, exudate almost like a diphtheritic throat, profound involvement of adjacent glands and prostrating toxemia. If of the many possible strains, the most prevalent is the beta-hemolytic, an almost sure therapeutic relief will come from sulfanilamide. Given by mouth in large primary doses with graded following doses, it is better to give with soda bicarbonate and to guard against blood reactions, by frequent study. It apparently should not be given with sulfates. Other strains and particularly the streptococcus viridans do not so respond and dependence must be principally placed upon typed transfusions.

STREPTOCOCCEMIA—FIRST TRY SULFANILAMIDE'

In closing this clinic I must express my deep appreciation to the earnest and helpful service of Dr. Louis E. Silcox in collaborating the details of this subject. Indeed he is almost entitled to a position of co-authorship. Perhaps, however, he will accept this tribute as sufficient commendation.

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THE PROPHYLAXIS AND TREATMENT OF ACUTE COLDS IN ADULTS

STRICTLY speaking adequate prophylaxis of the common cold does not exist. All methods used today fall far short of the mark of the 100 per cent success which we expect in such diseases as smallpox, typhoid fever and diphtheria. More and more information is being secured each year regarding the nature of this malady, but still prophylaxis is far from being attained.

The studies of Kruse¹ in 1914 and Foster² in 1916 gave evidence that colds could be caused by a filtrable virus. In the past five years the work of Dochez and his coworkers^{3, 4} have conclusively proved that a virus does exist in the individual suffering from either clinical influenza or common cold. In addition they have succeeded in transmitting the cold to man and laboratory animals, and have successfully propagated the virus in artificial media. Failure, however, has attended any attempts to build up immunity by virus administration to these experimentally acquired colds.

In spite of this evidence it is not yet fully conceded that the virus etiology of necessity applies to all colds. Thomson and Thomson⁵ point out that there is considerable evidence to show that bacteria, such as pneumococci, streptococci and influenza bacilli may of themselves produce colds. Shope⁶ has shown that in swine the virus alone will not produce the disease, but must be associated with a bacterium resembling the influenza bacillus in man. This bacillus itself without the associated action of the virus is powerless to produce symptoms. It is admitted by all that in the majority of colds there is a marked increase in the pathogenic organisms of the respiratory

tract within a few days after the onset of symptoms, and that it is in this stage of the infection that complications such as suppurative sinusitis, otitis media and infections involving the tracheobronchial tree are most likely to occur.

For practical purposes it will be satisfactory for us to divide the acute cold into two clinical stages: (a) The initial or virus stage and (b) the stage of bacterial activity. Undoubtedly occasional colds disappear without ever passing into the second stage. These are short-lived, may give rise to considerable local distress and systemic toxemia at the start, but tend to disappear in three to seven days without the appearance of a suppurative nasal discharge. If this type of discharge does occur, we may be sure that the stage of bacterial activity has been entered. At the present writing it seems fairly certain that no therapy of a specific nature exists that will secure immunity to the virus stage. If, however, anything is capable of reducing the virulence and length of the bacterial stage, it follows that the morbidity and complications will diminish in proportion to the effectiveness of the remedy.

The prevalence of colds is universal. In 1924 the United States Public Health Service⁷ sent questionnaires to 13,000 persons distributed from Massachusetts to California. In all localities colds appeared in epidemic form. A high incidence in October was followed by a fall until late December, when a sharp rise occurred reaching its peak in January. The influence of climate upon this condition is not so great as is generally supposed. Some years ago a survey was conducted which analyzed the incidence of colds in 900 college students selected from parts of the country climatically quite different. It was found that the proportionate number of colds in Pasadena, Galveston and Chicago was about the same. Another study comprised 5000 students selected from areas representing all types of climate found in the United States. Again it was found that the incidence of colds was about the same for the various regions. It was noted, however, that colds are unquestionably most frequent during that period of the year when sudden changes of temperature and humidity are most pronounced. Therefore, it is believed by many that climate itself is not of major importance, but that sudden weather changes can and do exert a profound effect on the occurrence of colds.

It seems to be true that acute colds may be acquired by two methods, from an outside source (exogenous), or from the development of the causative agent already present in the individual (endogenous). There are many examples of development of the cold following exposure to one already infected. On the other hand, many of us have contracted colds when no such contact occurred. With the latter type some sort of environmental change has usually taken place, the most common being overheating followed by gradual cooling, wet feet or clothing not followed by a prompt change to dry garments.

The question of treatment is possibly even more confusing than the factors previously mentioned. Vitamin feeding, sun lamps, roentgen therapy, chlorine inhalations, the use of alkalis, sweat baths, cold baths and vaccines (autogenous, stock and intra-oral) are only a few of the therapeutic and prophylactic measures used or still in use. The results of the use of vaccine as a prophylactic agent are varied. Certain observers have reported large series of cases in which the results of statistical analyses are definitely against the efficacy of the vaccine. In 1921 von Sholly and Park⁸ reported on their prophylactic vaccination of 1536 employees of the Metropolitan Life Insurance Company. They gave a stock vaccine in a series of 3 doses of 0.5, 1 and 1 cc. They concluded that the vaccination is worthless, because 29.7 per cent of their controls escaped infection, whereas only 13.7 per cent of the inoculated group had this experience. In 1927 Ferguson⁹ and his coworkers reported on a series of 138 treated patients, with 148 controls, and concluded that prophylactic vaccination with stock vaccines is useless and agreed with Jordan, Norton and Sharp,¹⁰ who contrasted the conclusions of satisfied patients and controlled statistics.

Many reports of vaccine treatment are, however, much more favorable than those mentioned. Eyre and Lowe¹¹ in 1918 treated 1000 New Zealand troops and used 1000 controls. The incidence of colds in those treated was 1.2 per cent against 7.3 per cent in the untreated. Given,¹² in 1921, using a vaccine supplied by the Royal College of Physicians of Edinburgh on sailors of the British Navy, found vaccination beneficial to from 55 to 65 per cent. Lempriere¹³ vaccinated 220 boys in a college of 535 students and found that the nonin-

oculated lost three times as much time from infections of the upper respiratory tract as the treated group. The severity of infection and of complications was noticeably reduced in the treated group. His treated patients, too, included practically all those in the school particularly susceptible to recurrent colds.

Thomson and Thomson¹⁴ after a thorough study of all the available bibliography on vaccination against colds stated:

"We will conclude that in our opinion there is abundance of irrefutable evidence in favor of the value of vaccines in the treatment and prevention of colds. Preventative inoculation against colds gives no guarantee of immunity to catarrh, but it is our experience that colds contracted in inoculated persons are less severe as a rule than those contracted by the non-inoculated, and furthermore, the inoculated are less liable to complications."

The literature is almost endless on this subject, and the references cited represent only a few of the most outstanding studies and opinions. At a glance it is seen that the subject is controversial and by no means settled.

Within the past four years an oral vaccine has been placed upon the market which is supposed to render the cold-susceptible individual less susceptible to colds. It is maintained that this remedy in a certain percentage of individuals increases the heterophile antibody content of the blood and in those so affected satisfactory results are secured. As yet no large series so treated has been reported by disinterested observers, and a critical attitude should be maintained until a well-controlled study of this product is available.

The prophylaxis of colds, therefore, falls into two general classes: (a) The avoidance of infection, and (b) the production of immunity. In considering the first heading, it follows that contacts with those infected should be avoided in an effort to prevent the exogenous type of infection. Proper clothing, avoidance of drafts and the taking of a hot bath after chilling of the body by exposure or wet clothing will do much toward preventing the endogenous variety.

With regard to the production of immunity it has been previously stated that so far nothing has seemed to confer any immunity to the virus stage of the cold. No harm, however, can follow the proper administration of a vaccine in the at-

tempt to prevent, shorten or lessen the severity of the bacterial stage. Autogenous, stock or oral vaccines may be tried. The common practice of 3 or 4 fairly heavy doses is less likely to produce results than smaller ascending doses carried over a long period of time. In fact, once having reached the maximum dose it is wise to continue monthly injections throughout the winter. The effect of sunlight, natural or artificial, vitamins, special diets and alkalis is certainly not specific.

Once the cold is established there is considerable truth to the statement that the treated cold lasts two weeks and the untreated one fourteen days. Sometimes it seems possible to abort the attack if the patient at the first sign of symptoms takes a hot bath, a diaphoretic and remains in bed until symptoms have subsided. In 1937 Rawlins¹⁵ published an interesting observation. Knowing that sulfur dioxide was potent in destroying virus diseases of plants, he applied this type of therapy to individuals in the early stages of acute colds. He found that in a series of 80 patients treated on the first day of a cold, 66 were completely cured in one or two days by inhaling the fumes of concentrated sulfurous acid. No results were secured if treatment was not applied during the first twenty-four hours of the attack. The writer has had no experience with this type of therapy, but feels that it should be given a trial by others.

Even though we admit that only rarely can an attack be aborted, a great deal can be done to increase the comfort of the patient. The widely heralded use of codeine and papaverine mixtures probably owe any efficiency they possess to the fact that it puts the patient to bed and makes him willing to stay there. Treatment naturally will vary with the severity of symptoms. All febrile cases should be confined to bed. It is almost impossible to force the busy male to bed if he has no fever, consequently many cases will be ambulatory. In the initial stages while the nasal discharge is profuse and watery, it is legitimate to use small doses of belladonna to secure a slight drying effect. Its use should be discontinued, however, as soon as there are signs of a yellow, purulent discharge. Small doses of benzedrine sulfate internally, 2 to 4 mg., often give some relief from nasal discomfort and at the same time combat the lassitude resulting from the toxicity of the infection.

If sleep is disturbed by this drug it should not be used. If tracheitis is present, mild counterirritants and warmth over the upper chest and neck add greatly to the patient's comfort. He should not sleep in a room colder than 60° F., for cold air acts as a constant irritant to an inflamed tracheal mucosa. Moist warm air is better tolerated, and toward this end inhalations of steam or the old-fashioned croup kettle can be used. Proper elimination should be maintained, but drastic catharsis, so frequently indulged in by the layman, is not necessary. Diet is of little importance so long as it possesses adequate fluid and food values and is easily digested.

Local treatment does little or nothing toward curing the disease. One need only study microscopic sections of the nasal mucosa during one of these attacks to understand why this is so. The nasal mucosa is markedly damaged, ciliary action is lost, the mucosa desquamates almost in toto, and the submucosa is edematous and filled with leukocytes. In other words, damage is so profound that only time and nature can repair it. In spite of this some local treatment may add to the patient's comfort and not act as a retarding influence in nature's efforts to repair the damaged structures. Antiseptics are worthless. Mild constricting agents can, however, be used to advantage. Neosynephrine, $\frac{1}{4}$ per cent, ephedrine sulfate, 1 per cent in isotonic solutions, are the least irritating of the constricting agents. Benzedrine sulfate by inhaler or solution is well tolerated by many. All these things if used at all should be used in moderation and only when necessary. It is wise to discontinue their use as soon as local nasal conditions permit. It is the feeling of the writer that no nasal treatment is better than overtreatment. Packs of colloidal silver and other antiseptic agents do nothing but add more irritation to an already irritated organ. Massive irrigations should not be used. Later in the suppurative stage gentle insertion of nasal tampons soaked in $\frac{1}{4}$ per cent neosynephrine and $\frac{1}{2}$ per cent cocaine hydrochloride may be indicated. This will produce considerable shrinkage and allow the escape of pus from nasal recesses and sinuses. Sometimes the use of a narrow suction tip will be of great value in removing these secretions.

Some inflammation of the mucosa of the paranasal sinuses is present in all attacks of severe coryza. If ventilation and

drainage can be maintained most cases will terminate spontaneously without development of the symptoms of acute sinusitis.

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AGRANULOCYTOSIS

THE case which we shall discuss today is one that is especially intriguing to me as it was here at Blockley that one of the first cases was diagnosed. In 1922 Schultz¹ described a new disease, later named "agranulocytosis" and Lovett,² Moore and Wieder³ soon reported cases and, of course, in such a great storehouse of medical lore as Blockley I was fortunate in finding one also. It took one year to get the record published because the editor of the medical magazine to which it was first offered was dubious about publishing the account without an autopsy report. My case⁴ was the third published in English following Schultz's original work. Since that time I have followed with interest the changes in medical opinion in regard to this disease. The one feature of this disease which is characteristic is the great reduction of the total white blood cell count with few and sometimes no granulocytes. The disease usually comes on suddenly with symptoms not unlike the grippe or a beginning tonsillitis. There is a marked muscular soreness all over the body with a high fever, often 105° F. and chills, coming on early in the disease. The patient feels extremely ill, looks toxic and the pulse and respirations are increased in keeping with the temperature. In the majority of the cases the pharynx is injected and there is pain on attempting to swallow. The glands of the neck are frequently enlarged but there is no general lymphatic enlargement. In one half of the cases jaundice of varying degrees of severity is seen. Small areas of necrosis of the skin may be seen and a rash on the chest resembling a dermatitis, sometimes a typical erythema multiforme, occasionally going on to a bullous eruption, has been noted at times. The fact that there is

no generalized lymphatic enlargement and that there is no tendency to hemorrhage in the skin (purpura) are important diagnostic points which we shall discuss later under differential diagnosis. The liver and spleen are not enlarged. The second characteristic physical finding after the blood count is ulceration. This occurs especially in the mouth and pharynx and may occur in the mucous membrane of any part of the body. The lesions described in the report of my first case are characteristic of a large majority of the cases. "The soft palate, uvula and anterior pillars of both tonsils were eroded and red. The superficial layers of the mucous membrane were involved and the line of demarcation between the healthy and diseased mucous membrane was abrupt without any surrounding areas of erythema. There was no exudate. The tongue and posterior wall of the pharynx were dry. There was some diffuse redness of the hard palate."⁴ This ulceration of the pharynx is accompanied by a fetid odor of the breath. It extends rapidly, sometimes going on to deeper necrosis. Edema of the glottis necessitating tracheotomy has been reported. Toxemia, heart failure and death occur in from forty-eight hours to one week.

Doctors were immediately struck with the fact that such an outstanding syndrome had not been described before. Only 2 clear-cut references to a similar condition have been found in the literature prior to Schultz's article: the case described by Brown in 1902 and one by Tuerk in 1907. Some cases of malignant sore throat described as diphtheria may have been agranulocytosis. The cases were examined for infection. Diphtheria was ruled out by culture and blood count. Vincent's spirillum and fusiform bacillus appeared locally in the lesions of many cases. The pneumococcus and streptococcus were also found. Blood cultures as a rule gave a negative result, but various organisms were found, especially *Bacillus pyocyaneus*. The multiplicity of findings indicated that no special organism was involved. When it was noted that the infection followed the initial symptoms and was really an indicator of lowered tissue resistance, we realized that bacteria did not cause the disease except in rare instances of profound overwhelming sepsis. As soon as the syndrome became well known the reported cases increased by leaps and bounds and

doctors said, "Surely, this must be a new disease. We have been making blood counts for years, yet we have not seen cases with such low white blood counts before." What new factors have come into our lives to create this new condition? Hamilton had found that benzol was a distinct industrial poison and that it caused leukopenia. It was suggested that its deleterious effects might be made use of in the treatment of leukemia. Kracke wondered if the benzene ring could be involved in agranulocytosis and Madison and Squire found that all their patients had taken amidopyrine and barbiturates. This immediately focused attention on drugs, and agranulocytosis cases, the result of various drugs, began to be reported. Subsequent study indicated that the barbiturates were not involved. Cases have been reported caused by phenacetin, cinchophen, atophan, dinitrophenol, neoarsphenamine, gold salts, quinine, sedormid, sulfanilamide, allonal, panoplen, pyramidon, aspirin, acetanilid, solganol, crysalbine, peralga, dial and many other similar drugs under various trade names. Those advocating the drug theory say that it is the tremendous increase in the use of the new coal tar analgesics that has caused this disease. This explanation was not satisfactory and others said,⁵ "We have given patients amidopyrine in large doses for years and none developed agranulocytosis. Amidopyrine is not the cause. It could not be the benzene ring because it appears in so many other innocuous drugs in nature. It is a wrong conception of chemistry that has led to its being so described." The problem has also been attacked mathematically by Rawls⁶ who studied the incidence of agranulocytosis during amidopyrine administration using the method of standard deviation and the mathematical mean and concluded that individual sensitivity and idiosyncrasy must be the basis.

Kämmerer⁷ and Pepper⁸ suggested that the important factor was allergy. Patch tests were made with the indicated drugs, but no response was obtained until Dameshek and Colmes⁹ advocated putting a solution of the drug in human blood and keeping it in the ice-box for several days. Tests made in this way were positive for amidopyrine. In some cases the patient had taken a drug for some time; then, after an intermission a small initial dose brought on the attack sug-

gesting that the body had become sensitized by the previous administration of the drug. A number of similar reports may be found in the literature. In order to test out the effect of amidopyrine, small doses were administered to patients who had recovered from agranulocytosis. They found that $\frac{1}{6}$ grain of amidopyrine was sufficient in such a case to start an attack, and they concluded that extreme hypersensitivity to amidopyrine must be present. This theory can be attacked in similar fashion to the theory that drugs cause agranulocytosis. In the past allergic people took amidopyrine and in some cases white blood counts were taken. Why did not someone notice this syndrome before? The fact remains, however, that the incidence of the disease is less since attention was called to drugs and allergy. The profession has become more alert to the danger of certain drugs and they are more alert to the significance of lesions in the mouth with the result that cases are found early and treated more promptly. This has resulted in a number of recoveries whereas Schultz described it as a fatal disease. It has also been found in the male although originally found only in the female. Another feature noticed in some cases that recovered is that the disease has had a tendency to recur at regular intervals. This cyclic neutropenia is supposed to be associated with the menstrual period. It is thought that drugs causing neutropenia, given at this time, accentuate the condition already present. The case of one young man is described whose blood has been studied regularly all his life from two and one-half months to twenty-five years of age. He has had recurrent neutropenia every month or so accompanied by some lassitude and malaise. This case may not be a true case of agranulocytosis. The author has done some interesting work on this young man's hormone excretion. He found that there was a cyclic hormonal fluctuation. The folliculin and gonadotropic hormones in the urine were studied in relation to the neutropenia and found to vary every twenty-one days. It was also found that injection of pentnucleotide aborted the next scheduled attack. The neutropenia preceded the fever which accompanied the attacks. Thompson¹⁰ then studied the relation of agranulocytosis to the menstrual period. He found that in 17 of 18 young women with agranulocytosis the onset occurred within a day or two of the regular menstrual period.

As the greater number of cases are found at or after the menopause and as other authors have not confirmed these findings, they may not be significant. In the Bucharest letter (J. A. M. A., p. 2021, 1938), under date of May 8th, Dr. Nitulescu is quoted as having noted that the administration of vitamin C hypodermically lessened the incidence of serum disease in children and also overcame intolerance to arsphenamine in persons who otherwise could not take it at all. Secher has noted that the administration of daily doses of vitamins A, B₁, B₂, and C to arthritis, prevents complications during the gold therapy.¹¹

There are numerous other references in the literature to the similarity between vitamins and hormones and to the fact that either or both of these products have an influence on allergy.

When we study the cases caused by drugs we find that some drugs which cause an agranulocytic picture in some cases affect other parts of the hematopoietic system in others, which would make it appear that agranulocytosis is but a stage in the poisonous effects of these drugs. This has led to the proposal to separate this class of "secondary" cases from the other or "true" agranulocytic cases, but even in these toxic cases it is evident that some common factor is at work because the patients have a predisposition or idiosyncrasy for the drug. Bismuth is an illustration. There are reports in the literature of agranulocytosis following bismuth. There are also reports of extensive ulceration of the pharynx followed by death in cases in which bismuth was given. We had one such case at Blockley last year. Recently¹² a report about the frequency of jaundice during the administration of bismuth for syphilis was written. Jaundice appears in about one half the cases of agranulocytosis. I would suggest that in Nomland's cases the jaundice represents a milder degree of toxic effect on the hematopoietic organs than in the cases in which bismuth gave a true agranulocytic syndrome. The same applies to arsphenamine. In some cases an agranulocytic picture is found; in others there is an anemia affecting red cells and platelets as well. The same point can be made about sedormid and the gold salts. There are several reports of agranulocytosis caused by them. The usual toxic effect of these drugs has been to

destroy the platelets, causing thrombocytopenic purpura.¹³ Cinchophen has caused a number of deaths from acute yellow atrophy of the liver. One of the characteristic symptoms of cinchophen poisoning is giant urticaria especially of the lips and pharynx and often causing edema of the larynx. I had a case with great edema of the lips and tongue before the toxic effect of the drug had been recognized. I wrote to one of the national drug companies about it. They replied that cinchophen was not known to have such an effect and that it was probably a case of food allergy. I recall discussing it with one of my students in the nose and throat section of the Post-Graduate School of Laryngology at the University of Pennsylvania, who had been in general practice at Tea Pot Dome (it was when this name was in the newspapers a great deal). He told me he had had 2 cases. In the second one he recognized that cinchophen was the cause. The first was diagnosed in retrospect. Agranulocytosis has been reported after taking cinchophen.¹⁴ It has also been reported in a case in which a patient, who fifteen years before had had giant urticaria attributed to seafood, took an unknown sedative. Both of these cases suggest allergic reaction to the drug given but the point that I want to make is that in all the above cases urticaria, purpura and jaundice have followed in some instances and agranulocytosis and death in others. Therefore, one should be exceedingly careful in the administration of medicine to such patients. In a certain number of cases of agranulocytosis it appeared that the administration of a protein precipitated the attack. Some of these records are old and one may argue that the authors did not know about the effect of amidopyrine or other drugs. Here again we can cull from the literature recent articles in which other parts of the blood-forming organs were affected, such as a case of thrombocytopenic purpura caused by injection of pertussis vaccine.¹⁵ One of the most interesting articles written on the subject of agranulocytosis, in my opinion, is by Francis T. Hunter.¹⁶ He points out that neutropenia may be found after foreign protein, serum or bacterial vaccine injections and after transfusion. Many such cases have chills, malaise, muscle soreness and an intense feeling of distress similar to that seen in agranulocytosis. That the liver may be affected in these cases is suggested by the

jaundice so frequently seen and the vacuolization and central necrosis of the liver reported at autopsy. He calls attention to the importance of the liver in pernicious anemia and repeats the thought that the maturation of the granulocytes in the bone marrow may be activated or suppressed by a secretion from the liver which may therefore have a rôle in agranulocytosis and which may be a basic factor in the cause of this disease. Hunter concludes, however, after an analysis of his cases that "there is not enough evidence in the literature or in the author's series of cases (27) to state that injury to the blood-forming organs from the use of drugs or foreign protein occurs more frequently in frankly allergic individuals than in normals, or oftener in patients with evidence of past liver injury than in those without it. . . . It may be allergic and may even be conditioned by functional damage to the liver." The examination of the blood in agranulocytosis shows a marked decrease in the number of leukocytes. They may be as low as 50. No case below 500 in Plum's¹⁷ series recovered, although some cases with lower counts have recovered. Plum gives a complete account of this disease. His monograph of 410 pages covers the ground thoroughly and includes a bibliography of 422 references. The granulocytes have frequently been entirely absent. This occurred in 90 per cent of Plum's fatal cases. "The granulocytes which are present in the fatal cases are most often degenerated, with vacuolated cytoplasm, poorly staining granules and pycnotic nucleus. In the patients who recover or die after hematologic improvement, the granulocytes look quite different, as they are largely young cells that may be designated—according to the usual classification—as premyelocytes, myelocytes, metamyelocytes and staff nuclears." In this instance the shift to the left indicates renewed activity of the bone marrow and is, therefore, a good sign. In the stage of recovery the granulocytes takes a heavy basophilic stain. Some authors think that an increase in the monocytes is a favorable sign.¹⁸ The lymphocytes are normal. There may be some increase in the plasma cells. The red blood cells and the platelets are normal in the typical primary agranulocytosis but in the secondary cases referred to above caused by the heavy metals or overwhelming infection, a decrease in the red count and the hemoglobin percentage may be found.

The examination of the bone marrow by sternal puncture has become an important diagnostic procedure. It has even been possible by this method to observe the disappearance of the granulocytes in the bone marrow before the blood was affected. Originally the marrow was described as aplastic. Custer,¹⁹ working at this hospital, was able to show that there is an actual hyperplasia of the bone in patients that recover. It has been considered that the disappearance of the granulocytes is due to a lack of the maturation factor which prevents the bone marrow from producing the granulocytes. It has also been suggested that the liver may produce some chemotactic substance which stimulates the bone marrow and activates the maturation of the granulocytes. This chemotactic factor may be the substance involved in the so-called "shock mechanism" and it may be the deficiency or aberration of some such factor that underlies allergy as a whole as well as agranulocytosis. The observations of Nitulescu about vitamin C quoted above may be pertinent.

The distribution and incidence of agranulocytosis brings up some interesting points for discussion. The greatest number of cases has been reported from the United States, Germany and Denmark. This has been attributed to the fact that amidopyrine has been used more extensively in those countries than in others. FitzHugh and Plum have shown for their respective countries that the cases began to be reported shortly after the use of amidopyrine became popular. Some authors have thought that it was more frequent in the well-to-do classes and especially frequent in doctors, nurses or their families. It would be interesting to note why these patients took the drug. In many instances it was for some form of rheumatism or arthritis. There has been no explanation to date to account for the fact that the majority of cases occur in women and most frequently in those at or after middle age. It has also been stated that many of these patients were allergic and had had episodes in their past history showing some such tendency, but nothing has been noted to date to account for the fact that it occurs more often in the plump, obese or better nourished patients. What is the significant factor in a plump, middle-aged, allergic female with painful muscles or joints that leads to the use of analgesics? About 20 per cent of the

cases have been reported in males and a few cases only in children. Although drugs undoubtedly can cause the disease as shown in the experimental work in which it has been used by administering them to patients that have recovered, there still remains the group of cases in which no drug has been reported, some of which have been seen since the effect of amidopyrine has been emphasized to the profession. We also should consider the report in which thrombocytopenic purpura with death resulted from the injection of *Bacillus pertussis* vaccine. We may consider this an allied disease although many authors have preferred to speak of true agranulocytosis in distinction from the cases which have hemorrhagic features and those which have been classed as aplastic anemia. A significant point is that the very same drug may cause any one of the above. I have not seen any reports, however, in which amidopyrine caused thrombocytopenia or aplastic anemia. A final point that would bear investigation is how many of the patients in which amidopyrine or other drugs caused agranulocytosis had also had bacterial vaccines or antigens administered. These were given to overcome infection. This infection has often been evidenced by a leukocytosis. Reduction of this has been interpreted as an evidence of the beneficial effect of the vaccine. Would it not be possible that the growing and widespread use of bacterial vaccines and antigens has been a factor in the development of these cases, especially in view of some reported cases in which they alone seemed to be the cause? Another point that is obscure is what is the mechanism which makes the lesions more or less selective for the mouth and pharynx. Can it be that there is any relationship between agranulocytosis seen, as a rule, in well-nourished people and often said to be among the professional class of physicians, lawyers, nurses, etc., and the well proved deficiency diseases, lately shown to be due to a lack of nicotinic acid in the case of pellagra and black tongue of dogs? In pernicious anemia and in sprue the involvement of the tongue with an aphthous stomatitis has long been known.

Among the blood changes we have a leukopenia with a tendency to lymphocytosis. Liver extract and ventriculin cure these diseases. That cinchophen can cause agranulocytosis

has already been referred to. It is interesting to note that it is used in dogs to produce experimental peptic ulcer.²⁰

Another point for study is the fact that agranulocytosis is seen often in cases of arthritis in which it has been presumed that the pain has led to the use of amidopyrine and that the unusual effect of this drug is due to allergy or idiosyncrasy. It is significant to me that in both these diseases a neutropenia and also a granulopenia is found with great frequency. Eosinophilia, so characteristic of allergy, is not found in agranulocytosis until the recovery stage at which time an "eosinophilia of cure" has been referred to. The local pharyngeal lesions of agranulocytosis can be differentiated from diphtheria, tonsillitis, Vincent's angina, apthous stomatitis by the smear, culture and, most important, the blood count, which should be taken in all ulcerative lesions of the mouth and pharynx. An increased number of monocytes during recovery is suggestive of agranulocytosis. The acute infectious diseases in which leukopenia is present, may give a picture in which the granulocytes are reduced to an extent resembling agranulocytosis, but the course of the disease and the characteristic symptoms of the infection will afford an evident clue in most cases. The cases of chronic leukopenia are often accompanied by a macrocytic or microcytic anemia which will differentiate them from a true agranulocytosis in which the blood count is said to be normal both before and after the disease. Aleukemic leukemia presents a picture at times that is impossible to diagnose from agranulocytosis. It is only by following the course of the disease and taking repeated blood counts, that a final diagnosis can be made. The disease is seen more frequently in young people and slightly more often in males. A study of the bone marrow may determine the diagnosis but not always. Aplastic anemia is accompanied by a marked degree of anemia, by involvement of the blood clotting factors with a low red cell count and lowered hemoglobin. In a typical case the difference from agranulocytosis is striking but in a mild case with lowered white count and granulocytopenia the diagnosis is not so easy. The cases of secondary agranulocytosis due to arsphenamine, radium or x-ray are likely to show signs of an aplastic anemia. The literature contains cases diagnosed agranulocytosis in which the red count was down, the platelets low and in which

purpuric spots appeared. These were better diagnosed aplastic. We have mentioned the confusion which these cases have created because the difference has depended upon the degree of the toxic effect of the drugs. Therefore, some clinicians have not considered these true cases of agranulocytosis, which they refer to as idiopathic. The trouble with the classification "idiopathic" is that here again we have the subdivision of those due to drugs and those in which the cause is unknown. Acute infectious mononucleosis is to be differentiated by the generalized enlargement of the lymphatic glands. In agranulocytosis the glands of the neck may be enlarged, but the other glands are not involved. The liver and spleen are not enlarged. The large lymphocytic cells of mononucleosis are not to be confused with the normal lymphocytes seen in agranulocytosis.

In a disease which occurs so rarely and which often progresses so rapidly it is difficult to evaluate treatment. It has not been possible to check carefully one series of cases against another and compare the result of treatment. Obviously antipyrine or any other drug that is thought to cause the disease should be withdrawn at once. Pentnucleotide, 10 cc. intramuscularly four times a day, has been widely used since it was introduced by Jackson. It increases the number of leukocytes. The expense of the treatment is a great detriment to its use in borderline cases. I have never known of a grave case in which it was not obtained, when asked for. Leukocytic cream is used instead of pentnucleotide and is preferred to it by some authors. Adenine sulfate, 20 cc. daily, intravenously, is recommended by Reznikoff. Nucleic acid has also been used. More recently glutathione has been suggested on the theory that the sulfhydryl radical stimulates cell division and may, therefore, stimulate the bone marrow to regenerate. It has not been tried extensively. Transfusion of blood should be tried in all cases. The objection has been raised that a 200-cc. transfusion will add very few granulocytes to the blood stream. Liver therapy should also be used. The objection to this has been that it particularly stimulates the production of red blood cells which are not involved in this disease. One case of agranulocytosis is reported occurring during the course of liver therapy. x-Rays have been widely used, although here as with the other measures used it is difficult to prove their value. Many cases

of severe aplastic anemia have followed x-ray therapy and some cases of secondary agranulocytosis have occurred. The treatment recommended is a mild stimulating dose over the long bones and sternum. The administration of 60 to 120 grains of fresh strained yellow bone marrow daily is said to be beneficial.²¹ Various bone marrow preparations are on the market.

That primitive man made use of the raw marrow is seen from this description of an Indian buffalo hunt. There were special parts that were eaten raw, immediately upon making the kill. The rest were carried off to camp to be cooked or to be preserved for future use. Francis Parkman in "The Oregon Trail" describes a scene just after the buffalo has been shot, "Some were cracking the thigh bones and devouring the marrow within. Others were cutting away pieces of the liver. . . . [They] proffered me a marrow bone so skillfully laid open that all the rich substance within was exposed to view at once." A part removed from the mouth was given to the smallest boy. Parkman did not see just where this came from.

Turpentine injections have been used to produce sterile abscesses to stimulate white cell production. One author advised the transfusion of blood from a leukemic patient. Leukemia has been produced experimentally in animals by the injection of leukemic blood.

Vitamin C and vitamin B have both been recommended. They should be given by hypodermic. The diet may also be arranged with them in view; therefore, asparagus, raw cabbage, raw tomatoes, kidney, wheat germ, egg yolks and fresh fruit juice may be ordered. Many of these patients have such severe throat involvement that they cannot take any food. They are so ill that it is imperative that they have good nursing. If sepsis sets in it is treated accordingly. Do not neglect the care of the mouth. Sodium bicarbonate, hexylresorcinol, and even sulfarsphenamine have been used locally to control the infection, especially Vincent's organisms.

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THE PROBLEMS OF THE POSTOPERATIVE GALLBLADDER PATIENT

THE medical treatment of gallbladder disease is no more important than the treatment of the gallbladder patient who has already been submitted to surgery. Owing to the popularity of operative intervention not only in the acute condition but as a solution for many of the problems regarding chronic gallbladder disease, gallbladder surgery is perhaps the most frequent source of operative intervention in the upper abdomen. The result is obvious. There are now an ever-increasing number of individuals in any cross section of the population who have had some form of gallbladder surgery. If these results were uniformly good there would be no need for further comment. That they are not uniformly good is apparent from our own experience and from practically all clinicians and surgeons who have had to handle many of these problems. In nearly twenty-five years one of us has had in private practice over 300 individuals who complained of trouble subsequent to gallbladder surgery and a cross section of hospital practice will reveal an increasing number of these cases. This does not mean that gallbladder surgery properly performed and in selected cases is not a brilliant and successful procedure. On the contrary it is probably one of the most satisfactory in the abdomen, second only but by no means equal to the success obtained by appendectomy.

No surgeon will deny that there are failures. Such a statement would only argue for inexperience in the face of the world's literature as it stands to day. There are failures and sometimes they are very serious so as to impose chronic invalidism. The failures can be classified somewhat as follows:

1. Improper selection of the patient.
2. Improper preparation of the patient.
3. Poor operative technic or complications incident to the many technical problems dealing with this subject.

In the first group, improper selection, we might divide this into three parts:

1. Incorrect diagnosis.
2. Associated disease.
3. Improper timing of the operation.

Incorrect diagnoses are by no means uncommon in gallbladder disease. By means of carefully controlled cholecystography and duodenal tube technic these failures in the actual diagnosis of gallbladder disease are markedly reduced. On the other hand the frequency with which other abdominal conditions occur and are frequently masked under symptoms similar to biliary tract disease demands that these associated conditions be clearly understood and if necessary receive adequate treatment. In other words, the problem is not merely the diagnosis of gallbladder disease but it might be enumerated as follows:

1. The demonstration of biliary tract disease alone as an entity requiring operation.
2. The possibility of associated disease in other viscera accounting for the condition of the patient.
3. The possibility that the associated condition is more definitely responsible for the state of ill health than the associated biliary tract problem. In the last instance biliary tract surgery will obviously fail to relieve the patient.

In our experience, the diagnostic problems frequently associated with gallbladder disease and not relieved by gallbladder surgery are the following:

1. *Appendicitis*.—In our experience many of these cases have already had an appendectomy. We have noted several instances, however, where symptoms were definitely referable to the appendix. Ordinarily the low-grade appendiceal problem creates comparatively little difficulty in the course of the operation for chronic gallbladder disease. The association with appendiceal inflammation via the duodenum and possibly the biliary tract and liver has been commented upon in the literature particularly by French observers. Furthermore the

appendix constitutes, when infected, a fixed focus in the abdomen. Under any survey of persistent digestive symptomatology, the status of the appendix should be considered. In each instance we make an x-ray study of the lower right quadrant.

2. *Peptic Ulcer*.—Peptic ulcer, more especially duodenal ulcer, is a fairly common association of gallbladder disease. In our own group the incidence has been relatively high. It is of interest to note that many of the chronic gallbladder symptoms may be duodenal in type and duodenitis is a very common condition in biliary tract disease. For that reason a patient with gnawing hunger pain and flatulent indigestion may reveal the exceedingly irritable duodenum of duodenitis with possible evidence of biliary tract disease, or he may reveal duodenal ulcer and gallbladder disease associated. We have had a rather large number of these problems and where this association occurs, it is necessary that the diagnosis be exact because the treatment of gallbladder disease may actually fail to control duodenal disease while the relatively high fat dietary used in duodenal ulcer may continue to aggravate the gallbladder. It is this association which explains many of the therapeutic failures where a duodenal ulcer exists. In most of these problems we use a dietary of the gallbladder type with in-between feedings and therapy directed to the control of the secretions. In severe cases, where there is a penetrating lesion with pronounced pain in the duodenum the early stage of the disease must entirely be controlled by the ulcerative phenomena. We have seen a number of instances where the diagnosis of duodenal ulcer was not substantiated but where the problem was plainly a biliary tract disease with duodenitis. Furthermore, the removal of the gallbladder will leave the resultant duodenitis as well as cholangitis unimproved. If the observer makes it a rule to follow carefully the evolution of the lesion (ulcer) by recheck with x-ray examination it is usually possible to demonstrate either an improvement in the lesion or failure in therapy.

3. *Cancer*.—Failure to diagnose carcinoma is a fairly common clinical mistake. Gallbladder disease, in particular, after an acute attack may result in pronounced loss in weight. If the loss of weight continues, one thinks of the possibility of

associated pancreatic disease. Nevertheless continued loss of weight with upper abdominal indigestion, particularly during middle life, always gives rise to the suspicion of malignancy. The three sources of malignancy are the stomach, the pancreas and the colon. Of these, only the pancreas is likely to be overlooked. Sooner or later, after unmistakable phenomena appear and it has been pointed out that in cancer of the head of the pancreas one may have a negative shadow with the cholecystogram. Painless jaundice, a palpable gallbladder, large fatty stools are characteristic of the disease at its height. Preceding its evolution, however, it may be masked by gallbladder phenomena. It is desirable that the surgeon be aware of the possibility of such a diagnosis. Fortunately the careful surgeon always explores the pancreas.

4. *Cholangitis*.—Cholangitis, when frankly associated with jaundice and recurrent signs in the upper right quadrant, is not difficult to appreciate. A low-grade inflammation of the ducts, however, is more difficult to diagnose. The testimony of the duodenal tube will probably do more than anything else to demonstrate the character of the bile obtained in this condition. Nevertheless, cholangitis with gallbladder disease should be given careful medical consideration before an operative solution of this problem is sought.

5. *Hepatitis*.—Hepatitis is a great battle ground in the question of biliary tract disease. There are those who believe that gallbladder disease does not exist without associated disease of the liver and there are some observations which lead to the belief that it is exceedingly uncommon. In any event surgery is not performed for hepatitis, nor is it desirable to perform surgery when the function of the liver is seriously compromised. The causes of hepatitis are manifold, varying from chemical, bacterial, allergic, to metabolic factors and the disease is an insidious one, scarcely recognized, unless careful liver tests are performed. The need for its recognition, however, is important because liver damage is a serious contraindication to operative procedure. Furthermore some of the French and German observers are of the opinion that associated hepatitis is the commonest single cause of failure in gallbladder operation.

6. *Pancreatitis*.—We have already referred to the pos-

sibility of pancreatic involvement. Unless this is pronounced, it is not easily recognized by ordinary clinical procedures. There are numerous claims that cholecystectomy cures many cases of low-grade pancreatitis. At the operating table the surgeon will recognize pancreatitis as an induration and thickening of the gland, which usually spells trouble for the patient. Where pancreatitis is severe, the patient may continue to lose weight and continue to have definite upper abdominal indigestion. Its presence can be recognized by quantitative duodenal tests as well as the pancreatic type of stool. It is usually treated by an appropriate diet and preparations to aid in food digestion and assimilation.

7. *Colitis*.—One of the commonest associations of gallbladder disease is a disturbance in colon function, namely constipation. In many of this group there is present evidence of some colitis. The mere fact that the portal vein drains the large bowel and the liver receives the impact of vitiated portal blood suggests the importance of this problem in the treatment of the biliary tract invalid. Chauffard in particular emphasized the importance of this problem in its repercussion on the liver cell, which would determine quality and quantity of the bile which was elaborated. Elsewhere we have pointed out that colon dysfunction frequently results in dysfunction of the gallbladder; as Lahey and Jordan pointed out some time ago. For this reason and because the bowel problem frequently persists after operation, it is necessary to direct attention toward that point. In our experience 75 per cent of our gallbladder patients were constipated or showed some signs of colitis or colon dysfunction. In the operative group that returned for treatment as long as ten years after operation, fully 65 per cent showed the same phenomena. It is furthermore apparent that the majority of these cases are spastic in type. For that reason treatment must be directed along certain lines:

- (a) Use of sedatives and antispasmodics.
- (b) Use of bowel-regulating medication.
- (c) The use of the modern substances used for demulcent and laxative effect.
- (d) Appropriate vaccine therapy where there is evidence of inflammation of the colon and bacterial resorption.

8. *Renal Stone*.—Renal stone has, in our experience, given

symptoms in the upper abdomen mimicking gallbladder disease. We now have a series of cases in which gallbladder disease and stone are associated. In one instance, an operation in the left ureter for stone precipitated an almost fatal attack in the right quadrant with severe liver insufficiency.

9. *Adhesions*.—Adhesions may occur in any part of the abdomen. They may be due to old abdominal surgery or they may be due possibly to a gradual thickening of bands which occur, but which through a mechanism somewhat similar to what Lane described, are due to a crystallization of lines of force or traction, which result in the formation of bands which impair visceral function.

Finally, one must bear in mind the possibility of diagnoses which may always explain abdominal phenomena, such as the crises of tabes, abdominal angina, lead poisoning and even some of the reflected phenomena associated with coronary vessel disease.

The question naturally arises as to how far the biliary tract must be damaged to necessitate operative intervention. Equally important is the time of intervention which will find the hepatobiliary tract in the best condition for such a procedure. In many instances, records of a careful history and physical examination and even careful duodenal and x-ray studies, the physician is hesitant as to operative procedure. Nearly one half of all gallbladders removed at the operating table are sterile, according to the testimony of the most prominent surgeons in the world. Therefore the argument that the gallbladder represents an active focus of infection is by no means so potent when one reviews the evidence. Furthermore the contention that the gallbladder once infected remains infected, is by no means a truism. On the contrary, the evidence from the experimental standpoint would suggest that infection would disappear from the gallbladder under appropriate conditions, just as it disappears from other organs in the body. We may speak of latent gallbladder disease but this expression is an ambiguous one. It fails to do more than simply visualize a shadowy concept of what is present and what may follow. Today there is a broad line of demarcation between gallbladders with stone and the stoneless gallbladder; surgeons are almost universally of the opinion that calculous cholecystitis

always demands an operative procedure and the majority of internists seem to share the same opinion. However, serious thought would indicate that there are cases of calculous cholecystitis that can be safely let alone and furthermore that there is a favorable and unfavorable time for gallbladder operation. It is absurd to lay down a clinical rule inasmuch as the physician is always compelled to individualize each particular case. Friedrich of Budapest pointed out so well some years ago, "Not too soon, and not too late, but select the right time for operation." Furthermore as Friedrich points out, the gallbladder is only part of the biliary tract, of which the liver and biliary passages are equally important. *Simply because the gallbladder with gallstones is removed, it does not follow that the liver and remaining biliary passages are healed*, nor does it follow necessarily that the gallbladder is a source of biliary tract pathology. On the contrary there is much to suggest that it is the end-result of factors which are clearly outside the domain of the gallbladder. Certainly a disturbed liver function and seriously comprised biliary tract are frequent aftermaths of gallbladder surgery.

From these observations it would appear that gallbladder removal is only justified when its function is hopelessly compromised. Certainly the physiological status of the biliary tract is altered. The extrahepatic radicles and, according to some observers, the intrahepatic branches are dilated. In a certain number of cases the functional status of that organ is not clear, but it seems probable that hepatic insufficiency frequently precedes and also follows cholecystectomy.

There is no question that indigestion and pain follow cholecystectomy and that it is by no means the ideal operation that appendectomy happens to be, for instance. Naturally this will depend upon the underlying factors presented by the patient as well as the technical difficulties resulting from the operation. Even some of the best surgeons fail to agree as to the best method of technic. According to Friedrich, there are two groups of surgeons: (1) Kehr, Diebold, Vere, Alapy, Kort, Finsterer, Huttner, who are likely to use the operation with drainage and the other group characterized by (2) Pribram, Bier, Hoffmeister, Haberer, Schutte, Mayo-Witzel, who close the abdomen primarily and claim that adhesions seldom develop

with the latter method. The frequency of pain following cholecystectomy is quoted variously by certain European authors. The large surgical statistics of Hotz give 20 per cent; Rhoda 19 per cent; Hintz 10 per cent; Lilk 32 per cent. From the standpoint of the internists, Umber 47 per cent; Bergmann 70 per cent; Lowenberg 21 per cent; Lumnitzer 2 per cent; Neuber 20 per cent. According to Friedrich 3 per cent of cholecystectomies are followed by distress or pain. Perhaps in a fairly large proportion of these cases, distress or pain is not due to the operation. There is probably another explanation. According to this author many other conditions like ulcer, appendicitis, colitis or pancreatitis were present. If we thoroughly study these cases, obtain a careful history, do a complete x-ray study of the entire digestive tract, fractional gastric analysis, duodenal intubation and urinary and blood studies, as well as functional tests of the liver, the explanation frequently becomes apparent. One is forced to the conclusion that these studies should have been made in many instances before operation, with greater profit to the patient. Certainly the findings frequently revealed by such an inventory would have been helpful to the surgeon and revealing as to post-operative treatment.

Physical examination might have revealed local tenderness and the presence of Head's zone. x-Ray studies may reveal ulcer, gastritis, colitis, appendicitis, diverticulitis, duodenal deformity as well as adhesions and spastic phenomena in almost any part of the digestive tract. Beclère, in the International Congress at Vichy, claimed that the duodenal bulb was always deformed following cholecystectomy. In the first series of studies which one of us made, 51 per cent showed fixation or deformity of the duodenal bulb. Duodenal drainage points to the possibility of associated cholangitis, duodenitis and even residual stone in the common duct.

Today we know, according to Friedrich, that the removal of the gallbladder does not lead to achylia, but that the latter is probably due to an associated gastritis. Following cholecystectomy, according to this author, anacidity is as common as hyperacidity, except that it is probably more significant of associated gastritis. This has been our experience. Friedrich found normal acidity in 48 per cent, hyperacidity in 29 per

cent and anacidity in 23 per cent. He made no distinction between the subacid and anacid groups. There is, however, no evidence, to our knowledge, to suggest that cholecystectomy produces anacidity. On the other hand, it is likely that the low acid group manifested similar acid responses before operation. Study of the stool, studies on the duodenal contents, the diastase and lipase, throw light on pancreatic function. The status of liver function is revealed by the bromphthalein test, the galactose sugar test and the bilirubin level of the blood as well as the urobilinogen study. A distinction must be made between biliary colic, such as might characterize a stone in the common duct and the simpler forms of indigestion such as flatulent indigestion, heartburn, distress or diarrhea, not at all uncommon in the interval of physiological adjustment. The former is naturally one of the most serious complications, characterized by pain, colic, jaundice and even Charcot fever due to an associated infected cholangitis. It has been claimed that symptoms due to adhesions appear much later following operation, but von Bergmann and his school claim that adhesions alone seldom induce distress. It is apparent in many cases over a lapse of years that the distress can hardly be due to adhesions alone. If there is anything which stands out in the foreign literature on this subject, it is the fact *that one must consider the possibility of residual disease of the biliary passage and liver.* Liver disease can arise through hematogenous channels, arterial as well as venous, through rare ascending infection and by lymphatic association. Our one hope of diagnosing cholangitis is by means of duodenal intubation, which may reveal bacterial and cytologic changes, indicative of a residual cholangitis and even the infecting organisms. On the other hand, the bile may be sterile and still there is present advanced changes in the ducts and even in liver function. Disturbances in pancreatic function as we have already described, can easily occur, following this operation, as Guleke, von Bergmann and Polya have pointed out. Following cholecystectomy, certain changes such as Westphal has pointed out may occur. In the absence of regular function of the gallbladder and a disturbance in the tonus of the sphincter, it is possible that bile might enter the pancreatic ducts and activate the pancreatic ferment. Apart from bacterial action one must con-

sider the possible influence of sterile bile. These observations by Westphal are significant of what might happen. While a residual stone in the common duct is the commonest cause of recurrent biliary colic, following gallbladder operation, the possibility of recurrent stone formation somewhere along the biliary passage, whether high up in the hepatic radicles or lower down in the common duct must also be considered. Added to this possibility are the inflammatory swellings, spasm or even organic deformity of the ducts themselves. It must be apparent that even slight anatomic change may occasion widespread functional disturbances. Rosenthal speaks of post-operative cholangiopathies. From these remarks it is apparent that we have the following possibilities after operation, each of which must be considered from the standpoint of the diagnosis and treatment of individuals who complain of upper abdominal discomfort due to residual stone in the common duct. This can occasion severe biliary colic in every way similar to attacks which the patient complained of before the gallbladder operation. Stone in the common duct may cause obstructive jaundice. On the other hand, as numerous authors, Judd and others, have shown, and our own experience would substantiate, jaundice may be entirely lacking, even during and following the attack, although there may be a slight rise in the serum bilirubin. The diagnosis of stone in the common duct is usually made by x-ray, which may or may not reveal a shadow. At times this is difficult or impossible. Duodenal intubation may reveal findings similar to those encountered in calculous cholecystitis; cholesterol crystals, calcium bilirubin, increase in leukocytes and mucus. But, on the other hand, we have found crystals with no evidence of stone in the bile of patients, following cholecystectomy. Biliary colic may be so severe and associated with cholangitis as to produce a classical picture with Charcot fever, chills, fever, pains and leukocytosis. The treatment of the common duct stone will be along these lines:

(a) The administration of adequate sedation and antispasmodic therapy.

(b) The use of the duodenal tube.

(c) A bland, low cholesterol dietary with plenty of fluids.

(d) Antisepsis, hexamine or salicylate therapy.

If the evidence is clear and medical relief fails to occur, surgery is of course indicated. If such an attack occurs in the hospital, following operation and there is an open fistula, the injection of lipiodol may definitely reveal the form and position of the stone. Such a film coupled with barium in the duodenum will enable the surgeon to localize fairly well the position and form of the calculus. We have had this experience on several occasions.

1. *New Stone Formation*.—There is no reasonable doubt that stones form in the biliary passages after the removal of the gallbladder. We have had this evidence in several cases; one in which, on three separate occasions, stones were removed from the common duct and recurred. That this possibility is not uncommon is our belief. Not every attack of biliary colic following cholecystectomy can be considered as a stone left in the ducts. It is probable that small calculi have migrated or new calculi have formed. In any event the treatment of such stones will be similar to that outlined for residual stone, but it is needless to point out that every means in our power should be carried out to improve the function of the biliary tract and liver.

2. *Cholangitis*.—Many European observers are of the opinion that this explains many of the phenomena not relieved by surgery. The diagnosis is most conveniently made with the duodenal tube and the bile fractions obtained show an increase in white cells, epithelial exfoliation from the ducts, inflammatory débris and not infrequently pure cultures of organisms known to produce biliary tract disease. The treatment of such a problem demands all those measures to improve colon function, stimulate liver activity, clear the ducts by means of the duodenal tube, the use of mineral water therapy and finally the various methods such as vaccine therapy and filtrate therapy, to improve the patient's resistance. It is always desirable to seek for other primary foci in the teeth, throat and bowel wall, in order to control or remove preexisting foci of infection.

3. *Hepatitis*.—The diagnosis of liver disease in these cases demands methods which will show only slight changes in function. Unfortunately most of our methods, the dye tests and the sugar tests are effective only when the liver function is seriously compromised. It is scarcely necessary to point out

their significance. Some observers claim that increased urobilinogen is a comparatively early finding. In any event one adds to this the icterus index and the quantitative van den Bergh reaction. Liver disease, more than any other type of visceral disease, demands a careful search of the habits, dietetic and otherwise, of the patient as well as the question of bile function. It demands a carefully arranged dietary, an avoidance of fatigue, a control of foci of infection, the very cautious administration of drugs, which are known to exert a toxic influence on the liver, such as cincophen, salvarsan, metallic poisons, barbiturates. It demands an improvement of biliary tract function and, most important, control of those factors which enter through the portal vein (bile function).

4. *Pancreatitis*.—We have before mentioned this possibility and also the method of treatment used in these cases. It is needless to point out that the pancreas can very definitely explain continued ill health on the part of the gallbladder invalid, the recognition of which demands certain dietary and medicinal adjustment.

5. *Duodenum*.—We have been particularly impressed with the duodenum as a cause of upper abdominal complaints. As before mentioned, duodenitis is an exceedingly common association of gallbladder and biliary tract disease, recognized by the appearance of the duodenum on the x-ray screen and the character of the material obtained by the duodenal tube. This demands practically the same treatment for ulcer of the duodenum; sedatives, antispasmodics, protective medication, small frequent feedings and even vaccine therapy. Apart from inflammations of the duodenum, which alter the mucosa of the organ, we also have deformities of the duodenum which follow gallbladder surgery. The first is fixation or distortion of the organ. The second is adhesions, going to the second or third portion, inducing angulation, puddling and even third portion delay. All of these are common every-day findings, for those of us who are called to study them. Where there is serious mechanical difficulty with definite gastric delay, surgery is the only solution to the problem. In many instances, however, the patient complains of heaviness, particularly after large meals; of regurgitation, heartburn, bloating and definite intolerance, frequently to fats or substances requiring long digestive

periods. This diagnosis can only be made on the x-ray screen and the competent observer will notice how far gastric function is compromised where there is real mechanical difficulty. The stomach picture may even resemble that of pyloric obstruction. In the ordinary cases, however, the difficulty is only partial obstruction. Finally, diverticula are not uncommon.

6. *Adhesions of the stomach*, fixing and deforming the pylorus and lesser curvature, inducing reflex gastric phenomena to the colon at or near the hepatic flexure. Verbrycke claims to be able to diagnose this disturbance by the shift in the angle of the colon, following the contraction of the gallbladder shadow after the administration of a fat meal. In any event, it is by no means uncommon to find adhesions coming from the gallbladder to the hepatic flexure of the colon inducing right colon delay and even reflex phenomena, which are very distressing to the patient.

7. *Colitis and Constipation*.—Both of these are common conditions with the gallbladder invalid and demand attention and care in their handling.

8. *Defective Fat Digestion*.—This must be due to pancreatic disease or a disturbance in the bile flow, following cholecystectomy. An increase in split fats is common in the feces and demands attention not only from the standpoint of the diet but also the administration of appropriate remedies to improve bile function and to aid digestion.



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DIAGNOSIS AND TREATMENT OF BACILLUS COLI INFECTION OF THE BLADDER

THE diagnosis of *Bacillus coli* infection of the bladder is at first sight very easy. It depends on two things. First, the usual signs and symptoms of inflammation of the bladder; and second, the identification of *B. coli* in the urine. Each of these two things, however, is much more complicated than it seems.

The usual signs and symptoms of inflammation of the bladder can be stated as painful and frequent urination, and pus in the urine. But obstruction as the neck of the bladder, which can occur in men, women or children, can cause painful and frequent urination—therefore, in any given case you must ask how much of these symptoms is due to obstruction, and how much to infection. Furthermore, infection of the kidneys may be present without pain or fever—therefore, in any given case you must ask whether the kidneys are infected or not.

You must also ask whether *Bacillus coli* is really the infecting organism or not. By "*B. coli*" we usually mean any member of the genus *Escherichia*, which includes at least 500 different species, all showing slight differences in cultural characteristics. In addition, there are at least 7 other genera of gram-negative bacilli found in the urine—*Aerobacter* (*aerogenes* group), *Proteus*, *Salmonella* (*paratyphoid* group), *Eberthella* (*typhoid* group), *Alcaligenes*, *Encapsulatus* (*Friedländer* group), and *Pseudomonas* (*pyocyaneus* group). Not one of these can be identified by any morphologic or staining characteristic, and their identification by culture requires skill and patience. Some of them, particularly the *Proteus*, *Encapsulatus*, and *Pseudomonas* groups, are resistant to the kind of treatment used for *B. coli* infections, and may

have to be handled differently. The diagnosis of "B. coli," therefore, must be confirmed by cultural studies.

It is my aim to demonstrate by these remarks that one must be very sure of his ground before saying that a patient has a *Bacillus coli* infection involving the bladder alone. Any physician who pays close attention to the above requirements will soon find that a *B. coli* infection involving the bladder alone is a rare thing, and that when it does occur, it usually disappears in a short time, even if no treatment is given. If it does not disappear within, at the outside, three or four weeks, the doctor may confidently inform the patient that he has more than a simple cystitis, that there is something keeping up the infection, and that further investigation is necessary.

The history, therefore, is a very important item. Did the patient suffer from "pyelitis" when a child? Have there been any previous attacks of "cystitis"? If so, how many, and when did they occur? Have there ever been pain in the back, chills, and fever? Is there any difficulty or frequency of urination between attacks? These and other similar questions show whether the infection is a new thing, or whether it has been present for a long time in a chronic, recurrent form. Unless it is a new thing, it is better not to waste much time in attempts at treatment, but to make a complete examination at once.

Study of the urine is very important. An excessive amount of pus indicates with certainty obstruction and stagnation somewhere; excessive numbers of bacteria have the same significance. The infecting bacteria must be identified. If pus is present, and no bacteria can be found, tuberculosis must be suspected. If neither pus nor bacteria can be found, vesical neck obstruction, neurogenic bladder, or interstitial cystitis (Hunner ulcer) must be suspected. The bacterial study is essential, as sometimes bacteria are found without any pus.

Physical examination may disclose an enlarged or tender kidney, enlarged ureters, or a distended bladder. On rectal examination, an enlarged prostate may be found. Vaginal examination may show an enlarged uterus or some pelvic mass.

After all these examinations, a catheter may be passed just after the patient has voided, to determine if residual urine is present, and how much. The bladder capacity should also be determined.

While the bladder is filled, the outer end of the catheter should be held as high as possible. If the urine flows out not at all, or only when the patient strains, bladder paralysis should be suspected. This diagnosis can be made definitely by a regular cystometric test.

The male urethra may be explored with a bougie-à-boule to detect stricture, and the female urethra should be calibrated with sounds, as a slight narrowing can maintain a chronic infection.

The first and simplest way of investigating the deeper structures is by x-ray. A plain film usually shows the shadows of calculi, if any are present. Intravenous urography is available to any physician and is often of the greatest assistance. There are a few precautions to take in interpreting the pictures obtained. If the shadows of the pelvis, ureter, or bladder are distinctly abnormal, or if they are entirely lacking, on one side or both, one can be sure that there is something wrong. If, however, the outlines are apparently normal, one cannot so confidently rely on these findings, as definitely diseased kidneys and ureters sometimes appear approximately normal in intravenous urograms.

Cystoscopy, ureteral catheterization, and retrograde pyelography can usually be relied upon to clear up the problem. Ureteral catheterization is the only way to find out whether there is infection of one or both kidneys. When pyelograms are made, the catheter should be drawn down into the lower ureter, and the ureter injected, so that a good picture of the ureter may be obtained, too. A cystogram shows trabeculation, cellules, or diverticula of the bladder, suggesting obstruction, or filling defects suggesting enlarged prostate or bladder tumor.

Finally, the ureters should be explored with bulbous bougies, as very slight narrowings may be sufficient to maintain a chronic infection. The normal adult ureter should admit a number 12 French bougie with no serious resistance.

A complete diagnosis may often be reached after only a few of these suggested procedures are carried out. The important point is that in practically every case of a *Bacillus coli* infection of the bladder which has persisted four weeks or more some definite obstruction or other pathological lesion will

be found, and unless this underlying lesion is properly treated, it will be extremely difficult or impossible to cure the infection. If the underlying lesion is not found and treated, the patient may get better, but only too frequently this improvement will turn out to be not a cure but only a remission, to be followed in due time by another acute attack. One should not be satisfied that a cure has really taken place until the urine is absolutely clear and sterile to culture.

I hope it is evident at this point that the diagnostic side is very important. I have emphasized it because successful treatment depends very heavily upon correct diagnosis. The indiscriminate giving of medicine or of irrigations for "cystitis" without any careful examination will, with few exceptions, lead to cure only in those patients who would have recovered without any treatment.

By far the commonest lesion underlying a chronic or recurrent *Bacillus coli* infection of the bladder is an obstruction of some kind. It may be at the ureteropelvic junction, along the ureter, at the ureterovesical junction, at the vesical orifice, or in the urethra. These statements apply to patients of both sexes, and of any age. I recently saw a male infant, five days old, with bilateral hydronephrosis and hydroureter due to a congenital narrowing of the vesical orifice. He promptly died of sepsis and uremia after infection was introduced on a catheter.

Of very special importance are the types of obstruction which tend to become progressively worse. One example of this group is prostatic enlargement. The methods of treating prostatic enlargement are now so safe and so successful that long delays in instituting such treatment are no longer justifiable. Surgical treatment is particularly necessary if infection is present, as the infection greatly increases the danger of inaction. Another example is the ureteral obstruction occurring in pregnancy. It is my belief that the urine of pregnant women should be routinely and frequently studied for infection. If infection is found, steps should be taken at once to combat the obstruction and eliminate the infection. This gives much better results than the usual procedure of waiting until the patient is severely ill with high fever before taking any action.

The treatment of the infection must include treatment of the underlying lesion. Obstructions must be relieved, stones and tumors removed. A badly damaged and infected kidney must be removed, if the condition of its fellow permits. If the underlying lesion is incurable, as for instance a complete paralysis of the bladder due to a spinal lesion, it is unlikely that the infection can ever be cured.

In considering the methods of treatment to be used, I shall first take up the methods of attacking the infection directly. These methods may be used in the acute stage of new infections during the first three or four weeks. The same methods are also used after the treatment of any obstruction or other underlying lesion, since the infection may persist even after the elimination of the underlying lesion. An example of this is the cystitis which often persists after a prostatectomy. The difference is that before the prostatectomy, no form of treatment will cure the infection, while afterward it will usually yield promptly to the proper treatment.

The growth of *Bacillus coli* in the urine has practically no effect on the reaction of the urine. Since human urine is usually acid, it will, therefore, remain acid if it is infected with *B. coli*, but the acidity is not due to the growth of the bacilli. *Bacillus coli* will also grow in alkaline urine, and for that reason alkalization of the urine usually is of no benefit whatever as a curative measure. In the past, bladder irrigations with various solutions were given routinely for *B. coli* infections of the bladder. We now know that the benefit, if any, from irrigations arose from the dilatation of strictures or narrowings of the urethra by the catheter used in giving the irrigation. For this reason, the passage of a few sounds will give equally good results, and in my own practice I abandoned bladder irrigations for the treatment of bladder infections years ago. In short, direct treatment of bladder infections has at the present time been reduced practically entirely to the use of oral medication. We have two exceedingly powerful urinary antiseptics, so-called, in mandelic acid and sulfanilamide. Both are effective against *B. coli*. Unless there is very definite evidence of an underlying lesion, such as an enlarged and tender kidney, a distended bladder, marked difficulty of urination, a stone shadow on an x-ray film, or some similar

sign, the administration of one of these drugs may be begun at once. With either of them, good results may be expected within a week or ten days if at all, and it is useless to continue giving the drugs for more than two weeks.

The manner of giving these drugs is now well known to the medical profession. Mandelic acid is given as one of its salts, usually calcium or ammonium mandelate. The urine must be kept very acid (pH 5.5 or less), giving if necessary ammonium chloride, and the fluid intake is to be kept low. The drug is apt to upset the digestion, and may have to be stopped on that account. When good results occur, they are usually rapid and dramatic. This drug has entirely replaced the ketogenic diet. Sulfanilamide is less distressing to the patient, but is more dangerous. It occasionally causes hemolytic anemia or agranulocytosis, and the patient must be watched much more carefully. The object of treatment is to create a fairly high concentration of the drug in the blood and tissues as rapidly as possible. To this end, large doses (60 to 100 grains a day, usually 80 grains) are given for one or two days, and the dose then rather rapidly and progressively reduced to from 20 to 40 grains a day. This dosage may be continued for weeks if no unfavorable symptoms develop. The drug is rapidly excreted, and it is therefore advisable to give a dose every two or three hours, instead of every six to eight hours as at first advocated. The fluid intake should be kept fairly low. Ten grains of sodium bicarbonate should be given with each dose, not to alkalinize the urine but to prevent acidosis. If the kidney function is impaired, large doses should not be given, but we now know that good results can be secured in such cases with much smaller doses.

If medicinal treatment does not produce a cure within three or four weeks, or if recurrence takes place, a thorough study should be insisted upon at once. This is really the most important message I can give you, and I have selected some cases for discussion to show how essential it is, and how the removal of the underlying lesion changes the infection from incurable to curable.

Before discussing the cases, I should say a word about focal infection. Many kidney and bladder infections are undoubtedly hematogenous in origin, and for these there must

be some kind of a focus of infection. I have seen dramatic cures of urinary infections following the removal of infected teeth or infected tonsils, but only too often the search for a focus of infection is fruitless. One may say, therefore, that a search should be made, but that the other considerations detailed here are usually of much greater importance.

Case I.—The first case I wish to present demonstrates how a slight obstruction serves to maintain a urinary infection. The patient is a married woman, aged forty-nine. She has two children, aged twenty-eight and twenty-three years. The labors were normal, and there was no kidney or bladder trouble with or following either pregnancy. The tonsils and all the teeth have been removed. Her medical story began two years ago with an attack of pneumonia. After this, the abdomen became enlarged, and an operation was performed. At this operation, a myomatous uterus and the ovaries were removed, and calculi were palpated in the gallbladder. Following the operation, catheterization was performed every eight hours for a week, and two weeks later frequency, burning, and a feeling of "pressure" over the bladder were noted. These symptoms continued for three months, varying in severity. In the worst periods, there was tenesmus, with extreme frequency and constant discomfort. There was occasional slight pain in the left back, but no chills or fever. On examination, neither kidney was palpable or tender. There was slight tenderness in both lower quadrants. The external genitalia appeared normal. A No. 18 catheter entered easily, obtaining 180 cc. of cloudy urine with large flakes of mucopurulent material. The bladder capacity was 550 cc. Study of the urine showed many pus cells and a large number of short, plump bacilli which belonged to the colon group.

These findings were so surprising that a No. 24 panendoscope was inserted under local anesthesia. The urethra was not greatly congested and no definite evidence of contracture or bar obstruction was seen. The entire bladder was acutely inflamed and edematous. Urine coming from the ureters appeared to be clear. It was thought that there must be some obstruction, and further studies were planned.

At the next visit, three days later, the symptoms were much improved. To my surprise, the urine obtained by catheter was crystal clear, and under the microscope showed no pus, blood or bacteria—in fact, it was entirely normal. The bladder was again examined by panendoscope, and it, too, had regained a normal appearance. Two more urethral dilatations were given with the Kollmann dilator, reaching a maximum of No. 38 French, after which the patient remained entirely well and free of symptoms.

The disappearance of the infection, which had begun as a catheter infection and which had persisted for three months, was truly dramatic. The effective cause of this disappearance was the passage of the panendoscope, an instrument of size No. 24; namely, 8 mm. in diameter. No other treatment was given.

Subsequent events confirmed this conclusion, and showed also that the relief obtained from mechanical dilatation may not be permanent. Almost a

year later, there was a return of symptoms, and a few bacteria were again found in the urine. Three dilatations of the urethra gave complete relief. After another year, exactly the same thing happened again, and again three urethral dilatations gave complete relief and the urine became absolutely normal. The obstruction in this case was so slight that it could not be seen, but it was very effective in keeping up the infection.

Case II.—The second case illustrates a similar situation in a male. More radical methods of treatment were, however, required. The patient was aged forty-one. He had contracted gonorrhea six months before, and the discharge had never entirely ceased, although it had become slight. He had voided twice at night since the beginning of the illness, and twice had passed a little blood. He complained of pain in the lower abdomen and burning on urination. He had been treated by massage and injections. Examination showed the stream rather small and weak, and the urine hazy with numerous flakes and small shreds. The prostate was moderately enlarged, quite firm, adherent, and slightly irregular. The secretion contained much pus, largely in clumps. The urine contained many pus cells and a large number of bacilli, which belonged to the colon group. The panendoscope showed the bladder not trabeculated, but inflamed, the mucosa of the base being thrown into great transverse folds. The vesical orifice grasped the instrument tightly, and appeared pale and irregular. There was no definite median bar, and the declivity was slight. The residual urine could not be determined. Rectal examination showed no definite indurated collar. The Wassermann reaction was negative. A short course of dilatation and massage produced no improvement, and the patient continued to have fever. After a retention catheter was inserted preliminary to resecting the orifice, the fever abated and the urine became clear at once, confirming the diagnosis of obstruction. The orifice was widely enlarged by transurethral resection. The tissue removed was firm, fibrous, and showed much mononuclear infiltration. The bladder infection never recurred after the resection. Healing was slow, with a little blood in the urine for two months. Three months after resection the urine was perfectly clear without shreds, and there were no symptoms whatever.

In this case the onset of symptoms coincident with an attack of gonorrhea tended to obscure the real diagnosis. It must never be forgotten that the persistence of a cystitis means that there is some underlying lesion, no matter how the cystitis may have begun.

Case III.—The third case is a somewhat bizarre one. In it the obstruction was much more severe than in the first 2 cases, but was even more difficult to demonstrate. After its removal, the disappearance of the infection was as dramatic as in the other 2 cases. The patient is a girl, aged sixteen. She has 13 siblings and there is no similar condition in the family. The most striking thing in the history is that the patient has always been a bed-wetter, and has

always had difficulty in voiding. At the age of six she had a painful swelling in the left loin, which was incised. Pus was evacuated and the wound healed promptly. In August, 1937, pain in the left loin recurred. A diagnosis of hydropyonephrosis and ureterectasis was made, and the left kidney was removed. It was also noted that the bladder was large and that there was a wide-mouthed diverticulum in the right upper part of the bladder. The incision healed in seven weeks, but following the operation the patient could not void and had to be catheterized. During this period she had a severe attack of acute illness, with chills, fever, pyuria and pain in the right side.



Fig. 175.—Cystogram, Case III. Note reflux in greatly dilated left ureter (left kidney has been removed), reflux in slightly dilated right ureter, trabeculation and small diverticula of bladder, extreme dilatation of proximal half of urethra.

When I first saw the patient, she was thin and anemic. The urine contained much pus, and large numbers of both bacilli and cocci. The bacilli were of the colon group. The nonprotein nitrogen was 32. The intravenous phenol-sulfonphthalein test showed an appearance time of ten minutes and an excretion of 35 per cent in thirty minutes. Cystoscopy disclosed marked trabeculation of the bladder, and several diverticular orifices. Both intravenous urogram and cystogram showed a diverticulum and reflux up the left ureter, which was still greatly dilated and tortuous (Fig. 175). On one occasion, there was a reflux up the right ureter filling the ureter and kidney pelvis. On the whole, however, the right side was in reasonably good condition. The cystogram also showed that there was a marked funnel-shaped dilatation of the juxtavesical urethra. Examination of this region with various kinds of instru-

ments showed nothing except a rather redundant, edematous and congested condition of the mucosa. The urethra could be dilated to size 35 with the Kollmann dilator, but the retention persisted.

There was also a marked spina bifida occulta, the entire sacral canal being open. Cystometric tests, however, showed a very strong expulsive power of the bladder, corresponding to that found in obstructed and hypertrophied bladders. The conclusion was, therefore, inevitable that there was an obstruction of some sort at a point opposite or just above the external sphincter. This had to be treated very conservatively in order to avoid the danger of substituting incontinence for retention. Coagulation was tried at first without success, but after a few small pieces had been removed with the punch instrument, she became able to void freely. Catheterization and cystogram showed that the bladder emptied completely with no noteworthy retention either in the diverticulum or in the dilated left ureter. Her voids reached as high as 450 cc. at a time and there was no frequency.

The urine has shown a remarkable spontaneous improvement so that there is now no pus and cultures taken ten days after the punch operation showed no growth.

It seems evident that the congenital obstruction of the urethra was the fundamental cause of all this patient's troubles. The case demonstrates how inconspicuous such a lesion can be, and how its existence can be predicated upon other evidence of obstruction, even when actual visualization of the obstruction is impossible. Again we see a dramatic spontaneous sterilization of the urine after removal of an obstruction.

Case IV.—The fourth case is that of a little girl, aged seven months. She suffered from painful and frequent urination and fever for nearly four months. When I first saw her she had been in the hospital for more than one month. She had received the usual treatment of alkalization and forcing fluids, then ammonium mandelate, and then sulfanilamide. The symptoms remained unchanged, and the urine at all times contained much pus and many colon bacilli. An intravenous urogram was unsuccessful, showing nothing diagnostic. Cystoscopic examination was then carried out, showing an inflamed bladder and a normal vesical orifice and urethra. The urine from both kidneys was heavily infected with *Bacillus coli*. In retrograde pyelo-ureterograms the kidney pelves were approximately normal, but both ureters were markedly dilated, especially in their lower portions (Fig. 176). There was evidently bilateral obstruction at or near the ureterovesical junction. With the pan-endoscope, it was possible to dilate both lower ureters to No. 7 French. Almost at once improvement began, and within two weeks the frequency had disappeared, the temperature had become normal, and the urine had become clear. She gained rapidly in weight and strength in spite of a bilateral mastoid infection occurring shortly after.



Fig. 176.—Bilateral retrograde pyelogram, Case IV. Note normal appearing pelves, marked dilatation of both ureters, normal bladder outline.

In this little girl, the infection was maintained in the kidneys by the ureteral strictures. The infected urine constantly coming down into the bladder kept up the cystitis. The same condition often occurs in adults, when, of course, it is completely useless to attempt to cure the cystitis by local treatment. One must always remember that an infected kidney may give no localizing symptoms whatever. In such case it can be found only by thorough urological study.

Case V.—The fifth case is included to demonstrate a similar situation in an adult, and also to show what a very powerful drug ammonium mandelate is. The patient is a woman, aged thirty-one. Urinary troubles began sixteen months before I saw her, with acute pain in the right side. A stone was found in the upper right ureter, and removed by operation. Nephropexy was also done. The convalescence was stormy and prolonged. Pain in the side continued. There were slight frequency and burning, and the urine was extremely dirty,

with a fetid, unpleasant odor. The ureter had been dilated a few times, but the dilatations always made the patient ill for two or three days.

The general examination was essentially negative. The operative wound was well healed. The urine was cloudy, with a fetid odor, and contained an

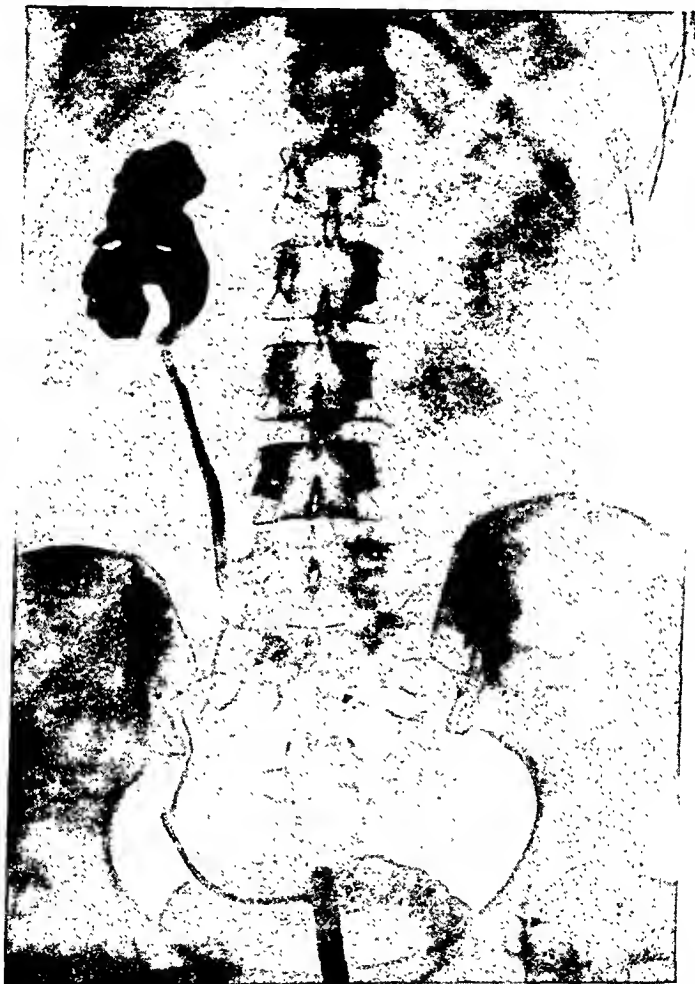


Fig. 177.—Retrograde right pyelogram, Case V. Note sharp narrowing at site of ureterotomy just below ureteropelvic junction, remainder of ureter approximately normal.

enormous number of colon bacilli, with comparatively few pus cells. This infection had persisted for six months, in spite of active treatment by a competent urologist. I gave ammonium mandelate, and examined the patient two

weeks later. At this time, the urine was clear and sparkling, and under the microscope showed no pus or bacteria. The fetid odor had disappeared four days after the medication was started.

The pain in the right kidney region continued in spite of the clearing of the urine. A pyelogram showed the kidney pelvis markedly dilated, due to a narrowing or stenosis in the upper part of the ureter (Fig. 177). Suffice it to say that the pain was finally relieved by repeated and quite radical dilatation of the ureter (size No. 17.2 French).

The important thing is that the ammonium mandelate eradicated the infection even while there was a definite upper ureteral obstruction and enough hydronephrosis to cause constant aching pain. This suggests that there may be some danger in the use of such powerful urinary antiseptics. If they are able to eliminate infections in the presence of obstruction, it may be that in some cases where the obstruction itself causes no pain, serious progressive damage to the organs above it can go on without the knowledge of the physician. To avoid this danger, an intravenous urogram at the very least ought to be taken in all cases, so that we may have some knowledge of the state of the urinary tract and of the existence of obstructions, if any.

The sixth case illustrates another interesting fact about bladder infections. It is that the infection may persist for some time after the removal of the underlying obstruction. This may be due to the presence of cellules or small diverticula, or to other causes with which we are not familiar. It is often seen after prostatectomy or prostatic resection. In such cases the new urinary antiseptics may be of great value.

Case VI.—The patient is a man, aged fifty-two. He presented himself a year and a half ago, complaining of frequent and difficult urination. Examination showed an enlarged prostate, and the urine was infected with *Bacillus coli*. Treatment was by transurethral resection. The operation was not complete, and more tissue was removed on two occasions. The symptoms, however, persisted. Very careful examination showed the prostatic obstruction thoroughly removed. The bladder capacity was 420 cc. and there was no residual urine. The urine, however, remained heavily infected, and the prostatic secretion contained much pus. The patient attended the dispensary for three or four months without any benefit; in fact, the frequency and pain increased. Treatment consisted of bladder irrigations and instillations, prostatic massage, and the passage of sounds. One month ago, ammonium mandelate was prescribed. Six days later no bacilli could be found in the urine, and the

symptoms were much improved. At the end of another six days, he was able to void 400 cc. of clear, sparkling urine which contained no pus or bacteria. He no longer had any pain, slept through the night without voiding, and considered that he was perfectly well.

With the weapons now at our disposal, very few cases indeed of bladder infection should fail to benefit from treatment. This will be true, however, only if the physician takes the attitude that the underlying causes must be sought out in every case of persistent infection. The search must be thorough, the searcher tenacious in his purpose, for the underlying cause is not always easy to discover. The physician may well be encouraged in his efforts by the recollection of how amazingly the outlook has changed for the patient with a urinary infection. Ten years ago, bladder irrigations and pelvic lavage were the standbys, and most of the patients who did not get well in a week or so never got well. At the present time, the urologist does not despair of any case unless the underlying lesion is incurable. Progress in this field has been as rapid and dramatic as in any field in medicine or surgery.

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THE MANAGEMENT OF MASSIVE HEMORRHAGE
FROM PEPTIC ULCER

ROBERT HUTCHISON, as Chairman of the Sections of Surgery, of Medicine and of Therapeutics and Pharmacology of the Royal Society of Medicine in London at their symposium on "The Treatment of Severe Gastric and Duodenal Hemorrhage" in 1924, said in closing the discussion that there was no medical treatment for hematemesis; that if the patient were put to bed and left alone, the results would be much the same. At the same time, impressed by some of the reports that had been made on the surgical treatment, he anticipated that within another decade there would be a swing toward more operations for this condition. Thus he challenged both internists and surgeons to devise an effective therapy.

Today, fourteen years later, Hutchison's challenge stands unanswered: the swing to surgery has not been realized and no effective type of medical treatment has been elaborated. In confirmation of this statement is the fact that within three months of this year we failed to stop the bleeding in 4 cases of peptic ulcer by medical procedures and in turn each of the patients died after expert surgical therapy.

This experience has led us to analyze the cases of massive hemorrhage from peptic ulcer observed in this hospital for the past twenty years (68 cases), most of them personally observed, and also critically to study the recent literature on the subject. We shall present in tabular form: (A) the important data on 5 cases in which the hemorrhage could not be controlled medically and in which surgical interference was undertaken as a life-saving procedure; (B) similar data on 14 operated cases, in all of which the hemorrhage had ceased beforehand and the operation was done under favorable circumstances; (C) certain statistical data on the entire group of 66

TABLE 1
PERSONAL CASES OPERATED IN MIDST OF HEMORRHAGE (5 CASES)

Identifi- cation.	Sex.	History.	Blood (lowest). Hb. %. R.B.C. (mil.).	Nonoperative treatment.	Operation.	Comment.
Date adm.	Age.					
L.K. S.11872 9/21/27	M. 42	Typical ulcer symptoms in 1919. Relatively free of symptoms then until hemorrhage few days before admission.	45 3.1	Transfusions; enteroc- lysis; liquid and soft diet; morphine; bella- donna.	10/7/27. Large gastric ulcer on lesser curva- ture. Ulcer oversewed; posterior gastrojejunos- tomy.	Persistent bleeding until operation. On second postoperative day had fatal massive hemor- rhage. Large eroded vessel found in base of ulcer (autopsy).
F.R. 32-12029 S.39149 4/5/38	M. 22	Typical symptoms for 5 years. Careless about diet. First hemorrhage day before admission.	20 1.5	Nothing by mouth for 1 day, then modified Meulengracht diet; Andresen diet later. Transfusion; venoclys- is; alkalis; morphine.	2/21/38. Penetrating posterior wall duodenal ulcer with large artery in base. Pyloric resec- tion and posterior gastrojejunostomy.	Continued to bleed for 2 weeks. Surgery re- garded as only remain- ing chance for survival. Died a week after op- eration of pulmonary emboli, probably sec- ondary to venous throm- bosis in arms.
H.P. 32-9771 S.24365 4/18/38	F. 25	Symptoms for 6 years. Gastro-enterostomy in 1932. Improved 1 year, then symptoms returned. Admitted 3 days after hemorrhage.	31 1.1	Nothing by mouth; transfusions; venoclys- is; Wangenstein drain- age.	4/29/38. Only marginal ulcer found. Posterior gastro-enterostomy taken down and ulcer resected.	Massive hemorrhage 6 days after operation. Died in 2 days. Au- topsy: large bleeding duodenal ulcer; opera- tive site normal. Also had pituitary tumor.

S.R. 37-26381 S.39628 6/21/38	M. 55	Symptoms 20 years previously; then free until shortly before admission. First hemorrhage after admission.	51 2.6	On Sippy diet when hemorrhage occurred; starved thereafter. Transfusions; venoclysis; morphine.	6/28/38. Small anterior wall duodenal ulcer, large penetrating lesser curvature gastric ulcer. Multiple ligatures around gastric ulcer. Posterior gastrojejunostomy.	Operation for continued massive hemorrhage. Bleeding not completely controlled at operation. Large eroded artery in base of gastric ulcer at autopsy.
P.F. 37-27547 6/29/38	M. 39	Symptoms for many years. Duodenal ulcer proved 1 year prior to entry. Careless about diet and mode of life. First hemorrhage before admission.	28 1.5	Starved for 1 day; milk and cream for 1 day, liquid and soft food. Transfusions; venoclysis; morphine.	7/6/38. Penetrating posterior duodenal wall ulcer found adherent to pancreas. Pylorectomy and posterior gastrojejunostomy.	Continued to bleed steadily. Operation undertaken as last resort with patient in poor condition. Died 3 days after operation of acute hyperthyroidism.

cases, including the 49 that received at the time or soon thereafter only medical treatment, and finally (D) a review of the literature with special reference to the form of therapy employed and the results obtained. Our primary aim is to determine what form of treatment is best suited to any particular patient with a bleeding peptic ulcer.

(A) PERSONAL CASES OPERATED IN MIDST OF
HEMORRHAGE (5)

Table 1 gives the significant facts in regard to the 5 cases that seemed to demand surgical interference in the midst of the hemorrhage. All of the patients died either from continued hemorrhage, or from complications arising during the early postoperative period. It will be noted that 2 of them were quite young (in the third decade of life), while only 1 was over forty-two years of age. Attention is directed to this age incidence because of the general belief that only the more elderly patients fail to secure a prompt cessation of hemorrhage on a conservative plan of treatment. Equally in disagreement with current opinion is the fact that none of them had had a hemorrhage preceding the one that led to operation; one of them developed his hemorrhage while in the hospital and on a Sippy program of treatment. The symptoms indicate, however, that ulcer had been present five or more years previously in each of them. This suggests that the ulcer may have been sufficiently callous to prevent retraction and closure of the open vessel. The degree of the hemorrhage is shown by the fact that the hemoglobin and red blood cells reached such low levels as 20 (per cent)/1.5 (million), 28/1.5, 31/1.1, 45/3.1 and 51/2.6. Because of our conservatism, shared by our surgeons, all were allowed to continue on a medical form of treatment for days to a week or more before we finally, in desperation, resorted to surgery. At operation the lesion was found to involve the posterior wall of the duodenum in 2 instances (F. R. and P. F.) and the lesser curvature of the stomach in 2 (L. K. and S. R.). In the fifth case (H. P.) only a gastrojejunal ulcer was found but subsequent autopsy showed that the bleeding had taken place from a large duodenal ulcer. In one of the gastric ulcer cases (S. R.) an additional but nonbleeding anterior duodenal wall ulcer was dis-

covered. In only 2 of the cases, both duodenal, was it possible to do a resection, thus removing the ulcer. In the anastomotic ulcer case death was caused by a massive hemorrhage from the associated but unrecognized duodenal lesion six days following the operation. In 1 of the duodenal cases (F. R.), in spite of his desperate condition at the time of the operation, during which he was given 2000 cc. of blood, he did well for a week and then died of pulmonary embolism. The other duodenal case (P. F.) died three days after operation in a state of acute hyperthyroidism. In 1 of the gastric ulcer cases (S. R.) the lesion had penetrated the posterior wall and the surrounding area could not be mobilized; sutures were introduced about the ulcer but, as autopsy showed, failed to reach the artery that had been eroded. In the other gastric case (L. K.) the ulcer was oversewed, but in spite of this a massive hemorrhage occurred on the second postoperative day and caused the patient's death. Thus death resulted in 1 from failure to discover the causative lesion; in 1, from a late pulmonary complication; in 1, presumably from a thyroid crisis, and in the 2 gastric cases, from inability adequately to deal with the surgical lesion. All, however, must be regarded as unavoidable surgical deaths and due chiefly to the desperate condition of the patients at the time of operation. The courage of the highly competent and skilled surgeons who undertook the operations is especially to be commended.

The error in the management of these cases probably consisted in the delay in bringing them to operation, the interval between hospital admission and operation being from one to two weeks in each instance. Autopsy in 3 of the cases showed a large eroded artery and it seems improbable that any of them had a chance of recovery except by surgery. That we shall refer to later.

(B) PERSONAL CASES OPERATED SUBSEQUENT TO CESSATION OF HEMORRHAGE (14)

Our second group (Table 2) consists of 14 cases operated after the hemorrhage had ceased. All were males and the ages ranged from twenty-eight to seventy years. Some had a short history (one had no symptoms prior to the hemorrhage that

TABLE 2
PERSONAL CASES OPERATED AFTER CESSATION OF HEMORRHAGE (14 CASES)

Identifi- cation.	Sex.	History.	Blood (lowest). Hb. % R.B.C. (mil.).	Nonoperative treatment.	Operative observations and procedure.	Comment.
Date adm.	Age.					
R.Z. S.61567	M.	Ulcer symptoms for 1 month. Slow hemor- rhage for 3 weeks. Bleeding on admission. Continued to bleed in hospital.	23 1.4	Nothing by mouth. En- teroclysis. Transfusion. Morphine. Atropine. Ice-cap to abdomen.	5/28/20. Gastric ulcer on lesser curvature. Cautery excision.	Satisfactory result.
A.F. D.D.A.W.	M.	Recurrent ulcer symp- toms for 25 years. Several hemorrhages, last one 1 month before entry.	30 3.0	Soft diet, belladonna, alkalis.	11/11/21. Duodenal ul- cer, posterior gastro- enterostomy.	No further bleeding be- fore operation. Was in good condition although hemoglobin was 45%. Subsequently had sev- eral hemorrhages. Died 1927.
D.J.McN. vol. 163	M.	Ulcer symptoms since 1921. Large hemor- rhage 3 days prior to admission.	14 1.2	Transfusions. Liquid and soft diet. Mor- phine. Atropine.	3/19/24. Acute duodenal ulcer, not excised. Posterior gastrojejun- ostomy.	Operated on after hemor- rhage had stopped and when blood count was satisfactory.
B.B. D.D.A.W.	M.	Ulcer symptoms for many years. Serious hemorrhage in 1920 and 3 days prior to entry.	34 1.9	Nothing by mouth. En- teroclysis. Morphine. Sippy regimen.	4/12/27. Old healed ul- cer at pylorus, a recent but healed ulcer in duodenum. Posterior gastro-enterostomy.	Never seriously exsan- guinated. At time of operation blood was in good condition. Left hos- pital in good condition.

V.A. D.D.A.W. 448 4/3/28	M. 51	No symptoms until day before entry. Sudden epigastric pain, followed by massive hemateme- sis.	70 4.1	Andresen diet.	4/23/38. Duodenal ulcer, bleeding slightly at time of operation. Ul- cer cauterized and over- sewed; posterior gastro- enterostomy.	In good condition when operated. R.B.C., 4.2; Hb., 80%. Never in alarming condition. Well 7 years later.
A.L.H. S.2686 2/19/29	M. 44	Ulcer symptoms for 3 years. Severe hemor- rhage 5 weeks before admission.	55 3.7	Sippy diet.	4/10/29. Two duodenal ulcers oversewed; pos- terior gastro-enteros- tomy.	Good result.
C.J.W. S.2953 8/23/29	M. 40	Ulcer symptoms for many years, recently aggravated. Hemor- rhage 5 days prior to entry.	50 3.1	Sippy regimen.	9/6/29. Duodenal ulcer, oversewed. Posterior gastro-enterostomy.	In good condition at op- eration. Satisfactory re- sult.
R.P. S.3519 9/18/31	M. 28	Ulcer symptoms for 2 years. Alcoholic. Hem- orrhage begun 9/9/31.	20 1.3	Conservative, with trans- fusions until hemo- globin 75%.	10/21/31. Ulcer with large crater on pos- terior duodenal wall. Active bleeding. Pos- terior gastrojejunos- tomy.	Excellent result.
H.H.W. S.3749 9/16/32	M. 70	Ulcer symptoms for 30 years, previous x-ray negative. Moderate hemorrhage 2 days be- fore admission.	70 3.5	Nothing by mouth. Milk and cream next day.	Duodenal ulcer. Pos- terior gastro-enteros- tomy.	A second hemorrhage in- hospital. Result satis- factory.
M. 11	53 3.1	Ulcer symptoms in 1932. Duodenal ulcer diag- nosed in 1933. Ad- mitted day after third massive hemorrhage.		Shock treatment. Trans- fusion. Venoclysis.	3/2/34. Duodenal ulcer. Excision impossible. Anterior gastro-enteros- tomy.	Died suddenly 9 days after operation in shock. Thought to have had a massive hemorrhage, but on postmortem no cause of death was dis- covered.

TABLE 2 (Continued)

Identifi- cation.	Sex.	History.	Blood (lowest). Hb. %. R.B.C. (mil.).	Nonoperative treatment.	Operative observations and procedure.	Comment.
Date adm.	Age.					
M.H.M. S.4038	M. 42	Ulcer symptoms in 1926, 1933, and 1934; last of 3 hemorrhages 2 days before admission.	74 3.9	Andresen diet. Aolin in- jections.	10/29/34. Large pos- terior duodenal ulcer. Posterior gastro-enter- ostomy.	Excellent result.
J.A.D. 33-14263 S.27605	M. 61	Ulcer symptoms for over 25 years. Repeated hemorrhages shortly be- fore one on Nov. 23, 1934.	40 2.7	Starved for 1 day. An- dresen diet thereafter. Morphine.	12/7/34. Two healed duodenal ulcers. An- terior wall ulcer ex- cised, Horsley pyloro- plasty.	Bleeding had stopped and blood picture had im- proved before opera- tion. Satisfactory re- sult.
J.C. 35-19275	M. 39	No ulcer symptoms prior to massive hemorrhage 4 days before entry.	36 2.2	Andresen diet. Trans- fusions. Iron.	12/30/36. Anterior wall duodenal ulcer, cauter- ized, oversewed. Poste- rior gastro-enterostomy.	Bleeding had stopped be- fore operation. Blood in good condition after repeated transfusions. Good result.
J.M.A. S.4831	M. 30	Ulcer symptoms in 1935 and 1936. Hemorrhages in Feb. and Sept., 1937.	40 3.0	Soft diet.	1/10/38. Two duodenal ulcers, more recent one on posterior duodenal wall. Ulcers cauter- ized; pyloroplasty.	In good condition prior to operation. Good re- sult.

began on the preceding day and led to his admission), but most of them had had typical symptoms of ulcer irregularly for years, 2 for twenty-five years, and many had had previous hemorrhages. The studies in many instances showed as great blood loss as in our first group. Some had bled for days before admission and continued to bleed in the hospital. A waiting policy, again agreed to by our surgeons, was rewarded in these cases by an eventual cessation of the bleeding. Then, when their condition seemed to justify operative interference (five days to a month after admission) they were subjected to surgical management. Thirteen of them had a duodenal ulcer and of these, 3 had 2 duodenal lesions and 1 had a duodenal and a gastric ulcer; 1 other case had a gastric ulcer on the lesser curvature. All but 1 (93 per cent) survived and subsequently were discharged in satisfactory condition. The one (O. P.) that died (nine days after operation) was thought to have had another massive hemorrhage, but autopsy revealed no hemorrhage or other satisfactory explanation of his death.

From a consideration of this group alone one is forced to conclude that operation should be delayed, but we have seen that such delay sometimes results in a fatality. The problem, therefore, is to decide, if possible, which cases treated conservatively will bleed to death and which ones will finally stop bleeding. Again let us postpone a discussion of that question, and, before referring to the data and opinions of others for help in the decision, let us consider our total series including the 49 cases that were managed throughout on a nonoperative basis.

(C) TOTAL SERIES OF PERSONAL HEMORRHAGE CASES (68)

Because of the facts that only 5 of our total series required surgery in the midst of their hemorrhage and because they apparently were of the same type otherwise as the 14 cases operated after the cessation of hemorrhage and as those never subjected to surgery, we are considering here the entire series statistically rather than the 49 nonoperated cases alone.

Of the 68 cases, 56 were males and 12 females, giving a ratio of 4.7:1. Seventy-five per cent of the cases were between thirty and sixty years of age. Twenty-one of the cases were admitted to the hospital on the day the hemorrhage was

recognized; 7, on the second day after the beginning of the bleeding; 6, on the third day; 8, on the fourth day, and all but 15 of the cases within ten days. Many of them had had previous hemorrhages, some irregularly for years. The extent of the hemorrhage is shown in Table 3, which presents the hemo-

TABLE 3

LOWEST HEMOGLOBIN AND RED BLOOD CELL ESTIMATIONS IN TOTAL PERSONAL SERIES

Hemoglobin.		Red blood cells.	
Per cent normal.	No. of cases.	Millions/cu. mm.	No. of cases.
Less than 20	1	Less than 1.5	2
21 to 30	13	1.5 to 2.0	17
31 to 40	13	2.0 to 2.5	8
41 to 50	8	2.5 to 3.0	13
51 to 60	17	3.0 to 3.5	17
61 to 70	9	3.5 to 4.0	8
71 to 80	7	4.0 to 4.5	3
Totals	68		68

globin percentages and red blood cell counts. Although some had only moderate anemia, all were admitted because of an acute hemorrhage, indicated by hematemesis or profuse melena. At least one half of them at the time of admission showed some signs of shock.

The medical management varied somewhat, but, with the exception of 2 cases treated by the Meulengracht technic, it was routinely of a very conservative nature. Excluding those two cases, all of those admitted in the midst of a hemorrhage or soon afterward were given nothing by mouth for forty-eight hours or more and morphine hypodermically in sufficient dosage to allay restlessness. When the clinical condition suggested that the bleeding was active and especially when the pulse rate was rising and the blood pressure was steadily falling, small blood transfusions were given, but these were not frequently repeated. In some instances saline and glucose solutions in small amounts were cautiously injected intravenously. After the second day, even in some instances when we were not certain that the bleeding had stopped, small frequent feedings by mouth were begun. These usually consisted of the Andresen gelatin mixture or of the Sippy milk and

cream mixture. Later, when the patient's condition seemed stationary and there was no evidence of further hemorrhage, other soft foods were added, but always the frequency of the feedings was kept up for several weeks, and meats, the coarser vegetables, raw fruits except orange juice, and acid substances were prohibited. Alkalis were administered in some instances, but during recent years we have rarely employed them because, usually, we find the feedings are sufficient to maintain neutralization of the gastric acidity and that the patients are more comfortable and obtain equally satisfactory healing of the ulcer without them. When pylorospasm was suspected or the stomach for any reason did not seem to be emptying itself satisfactorily, belladonna was given in adequate doses, but this also was avoided unless clearly indicated, because of the disagreeable dryness of the mouth. Mild sedatives, such as the bromides and barbiturates, were employed freely and, we believe, are of great value. Iron was given by mouth in most of the cases to hasten the regeneration of blood.

In 2 cases, as stated, the Meulengracht treatment (to be discussed later) was employed. In one of these it was begun in the midst of the hemorrhage and after one day of starvation: it had no influence whatever in bringing about a cessation of the bleeding. That patient was finally operated on and had a large posterior duodenal wall ulcer, still bleeding, and he died subsequently. The other patient, admitted on the day following a moderate hemorrhage, was first starved for two days, then put on the Andresen diet for one day, and finally, because he disliked the gelatin mixture, was put on a full diet including ground meat. He promptly felt better and had a satisfactory convalescence. Roentgenological study later showed a large duodenal ulcer and he made a good recovery without surgery.

The roentgenological diagnoses were as follows:

Diagnosis.	Number of cases.
Duodenal ulcer.....	47
Gastric ulcer.....	4
Duodenal and gastric ulcers.....	2
Gastrojejunal ulcer.....	3
Probable ulcer.....	2
Not x-rayed.....	10
Total.....	68

¹ Of these, operation showed that 3 were duodenal and 1, gastric.

In the total series the diagnosis was finally confirmed by the roentgen ray or at operation in 62 instances. The lesion was duodenal in 52, gastric in 7, gastrojejunal or anastomotic in 3. Thus 84 per cent of our proved bleeding ulcers were located in the duodenum. This predominance of duodenal over gastric lesions is in agreement with the data from other American sources, but in sharp contrast with English statistics, as shown in Table 4.

TABLE 4

DATA ON THE ANATOMIC LOCATION OF BLEEDING PEPTIC ULCER IN AMERICA AND ENGLAND

Authors.	Gastric.	Duodenal.	Anasto- motic.	Total.
	Number.	Number.	Number.	Number of cases.
	Per cent.	Per cent.	Per cent.	
English:				
Aitken.	$\frac{11}{58}$	$\frac{7}{37}$	$\frac{1}{5}$	19
Cullinan.	$\frac{30}{73}$	$\frac{11}{27}$..	41
Hellier.	$\frac{119}{63}$	$\frac{52}{28}$	$\frac{17}{9}$	188
Hurst and Ryle.	$\frac{54}{66}$	$\frac{21}{26}$	$\frac{7}{8}$	82
American:				
Lineberry and Issos.	$\frac{4}{10}$	$\frac{32}{84}$	$\frac{2}{6}$	38
Allen.	$\frac{42}{29}$	$\frac{94}{65}$	$\frac{8}{6}$	144
Miller and Elsom.	$\frac{7}{11}$	$\frac{52}{84}$	$\frac{3}{5}$	62

Only the results in the 49 nonoperated cases deserve separate mention. Three of them, 6.1 per cent, died, whereas all

of the others made a good temporary recovery. Of the 3, 1 had a perforation and the other 2 died of continued profuse hemorrhage.

(D) DATA FROM THE LITERATURE

We have divided the cases of which we have found reports in the recent literature into two large groups: those subjected to surgical management (Table 5) and those treated nonoperatively (Table 6). This in some instances has necessitated separating the cases reported by a single author.

It will be observed (Table 5) that we found records, including our own, of 383 operated cases and that of these 107, or 28 per cent, died soon after operation. The mortality percentages for the individual authors vary from Finsterer's 5.9 to Bulmer's and to Cullinan and Price's 100. Rarely are definite statements made to indicate whether or not the operations were performed in the midst of the hemorrhage and, if during the hemorrhage, whether they were done early or late in the course of the bleeding. Our personal data, however, show such a decisive difference in the results based on those factors that it seems necessary to consider them if we are to make a just appraisal of the individual results. It is desirable, therefore, to search for further information on these points.

Fortunately some estimation of the situation is possible. Finsterer, for instance, who has the lowest mortality (5.9 per cent), favors early operation (within twenty-four to forty-eight hours) in all bleeding cases. Thus he must include in his series all the cases that would have recovered on a medical program or with delayed operation. His results show simply that with early operation the mortality may be kept low. Allen also reports a low mortality (14 per cent) but he in most instances delays operation until the hemorrhage has ceased, as in our second group of 14 cases; furthermore, when he does operate in the older patients, he does so early, within forty-eight hours, and doubtless includes some that would have recovered anyway. In this latter group his mortality is $33\frac{1}{3}$ per cent. Of the English surgeons, Gordon-Taylor has the best results, and he too operates within the first or second day. Ross also operates early in the profuse hemorrhage cases, but his mortality rate is high. On the other hand, the more

TABLE 5
DATA FROM THE LITERATURE ON OPERATED CASES OF PEPTIC ULCER HEMORRHAGE

Author.	Reference.	Number of cases.	Deaths.		Comment.
			No.	Per cent.	
Wright, Garnett.	Proc. Roy. Soc. Med., 17: Part III, 29, 1924.	7	3	43	All in critical condition. None operated for first hemorrhage.
Patterson, H. J.	Proc. Roy. Soc. Med., 17: Part III, 29, 1924.	19	7	36.8	Operated in various London hospitals. All cases of acute bleeding.
Lynch, R.	Canad. M. A. J., 17: 677, 1927.	21	9	42.8	Avoids transfusion if possible. Total series, 52 cases.
Crohn, B. B.	"Affections of the Stomach," W. B. Saunders Co., Phila., p. 627, 1927.	7	5	71.4	Total series, 101 cases. Massive hemorrhage in each case.
Ross, K.	M. J. Australia, 1: 168, 1930.	43	26	60.4	Favors early operation, even after first hemorrhage. All profuse hemorrhage cases.
Bulmer, E.	Lancet, 2: 720, 1932.	2	2	100	Total series, 578 cases.
Cullinan, E. R. and Price, R. K. 5	St. Barth. Hosp. Rep., 65: 185, 1932.	4	4	100	Total series, 105 cases. Advise conservative treatment and avoidance of disturbing therapeutics.

Author	Year	Source	4	3	75	Total series, 202 cases. Transfusion only for repeated hemorrhage. Surgery only after four hemorrhages.
Hellier, F. F.	7	Lancet, 2: 1271, 1934.	21	7	33.3	Total series, 255 cases. Massive hemorrhage in each operated case.
Aitken, R. S.	5	Lancet, 1: 839, 1934.	6	5	83.3	Total series, 391 cases.
Davies, T. A. L. and Nevin, R. W.	10	Brit. M. J., 2: 858, 1934.	32	6	19.2	Operated on first or second day of bleeding.
Gordon-Taylor, G.	8	Lancet, 2: 811, 1935.	51	3	5.9	Hemoglobin 20-30 per cent in each case.
Finsterer, H.		Lancet, 2: 303, 1936.	2	1	50	Total series, 38 cases. Massive hemorrhage cases. No deaths in 36 medically treated.
Lincherry, E. D. and Issos, D. N.	7	South. M. J., 30: 1228, 1937.	1	1	100	20 other cases treated medically (Meulengracht) and lived.
Witts, L. J.		Brit. M. J., 1: 847, 1937.	144	21	14.6	Most operations after recovery from hemorrhage but after 2 days in elderly; mortality 33 per cent after 50 years of age.
Allen, A. W.	10	Surgery, 2: 713, 1937.	19	6	31.5	Five operated late in the hemorrhage; one, after an interval without bleeding.
Miller, T. G. and Elsom, K. A.		This report.	383	107	28	
Totals						

conservative physicians and surgeons, who first give their patients a chance on a medical regimen, such as Wright, Lynch, Crohn, Hellier, Davies and Nevin, and as we have done, report a high operative mortality.

Thus it seems clear that the operative mortality rate varies directly with the lateness of the operation in the course of the bleeding. This probably indicates, as in our own series, that those patients who do not stop bleeding after conservative treatment are operated on under conditions unfavorable for survival. If, however, operation is delayed until the hemorrhage has been controlled and until the general condition of the patient has improved the mortality is low, no greater, as we shall show, than in the cases kept on a medical program.

The data consequently suggest that only the cases that will not stop bleeding on a conservative medical program should come to operation during hemorrhage, but that at the same time those cases should be operated within twenty-four to forty-eight hours after the onset of the hemorrhage: this involves an almost impossible prognosis. Let us, however, review the available data on the cases treated medically, to determine, firstly, the average mortality without any surgery; secondly, what medical regimen is most likely to lead to a cessation of hemorrhage, and thirdly, what means, if any, are available for an early opinion as to whether further conservative treatment is justified.

Table 6 gives the significant data from the same and additional publications on 5843 cases treated nonoperatively. Of these, 508, or 8.7 per cent, died while under observation and because of hemorrhage or its complications. This mortality is to be compared to 28 per cent for the operative cases from the literature and 31.6 per cent for our operated cases. In our 49 nonoperated cases the mortality was only 6.1 per cent.

Further analysis shows that the mortality for the nonoperated cases varied from none to 25 per cent. Seventy-one cases are reported by 3 authors with no mortality and 35 of these were treated by the Meulengracht technic. Meulengracht himself has treated 368 cases by his method and with the next lowest mortality, 1.3 per cent. In all, our table includes data on 509 cases so treated, with a mortality of 1.8 per cent.

Meulengracht's program of management, therefore, demands special consideration. First outlined in 1935, and in general agreement with the regimen proposed by Andresen in 1927, though his paper is not referred to, it consists of 6 feedings daily from the onset of the hemorrhage, the food consisting of tea, bread and butter, oatmeal, ground meats and vegetable purees. He also gives an alkaline powder with hyoscyamus, three times daily, and ferric lactate. His regimen is alleged to be based on the following personal observations and opinions: (1) that exhausted patients often die of hemorrhage in spite of scrupulous dieting, (2) that sometimes patients with protracted hemorrhage stop bleeding when fed, (3) that ambulant patients often recover from severe melena without dietary change, (4) that starvation is of questionable value in a patient in need of support, (5) that an empty stomach with free acid may be harmful and (6) that a diet insufficient in calories and vitamins is not ideal for promoting the healing of ulcers.

Some of these personal opinions are not susceptible of objective proof, but the facts that in one third of his cases the bleeding had led to a reduction of the hemoglobin to 50 per cent or less, that all of his cases were considered severe and that 3 other workers have obtained similarly good results would seem to demand a further trial of his regimen. It is possible, of course, that he was dealing in the main with cases of diffuse gastritis with superficial erosions, which is common in the Scandinavian countries, rather than with typical ulcer as we know it. It is certain that he did not encounter many cases with large open arteries such as were present in our 5 operative and 2 nonoperative cases that died. Further reports from this country and England, where ulcers tend to be more deeply penetrating, would seem necessary before undertaking the technic without great caution. In 1 of our 2 cases in which it was tried no beneficial effect was observed and the patient finally came to operation.

The only other series with no mortality is that of Lineberry and Issos, who reported 36 cases, all fed from the time of admission to the hospital. They, however, were given only milk and cream, together with alkalis, in accordance with the original Sippy program.

TABLE 6
SUMMARIZED DATA FROM THE LITERATURE ON MEDICALLY TREATED PEPTIC ULCER HEMORRHAGE CASES

Author.	Reference.	No. of cases.	Deaths.		Treatment.	Comment.
			No.	%		
Years covered.						
Patterson, H. J.	Proc. Roy. Soc. Med., 17: Part III, 1924.	120	4	3.3	Conservative with operation in some later.	.
Crohn, B. B. 10	"Affections of the Stomach," N. Y., 1927.	94	4	4.2	Conservative with transfusions.	All severe cases.
Lynch, K. 10	Canad. M. A. J., 17: 677, 1927.	31	4	12.9	Nothing by mouth for 48 hrs.; then Sippy diet.	Fears transfusions.
Bulmer, E. 30	Lancet, 2: 720, 1932.	576	60	10.4	Conservative with transfusions.	Male: Female = 2:1.
Chiesman, W. E. 6	Lancet, 2: 722, 1932.	191	48	25.0	Conservative.	No deaths from 1st hemorrhage.
Cullinan, E. R. and Price, R. K. 5	St. Barth. Hosp. Rep., 65: 185, 1932.	101	15	14.8	Conservative with transfusions.	Advises conservative treatment. Avoidance of disturbing therapeutics.
Wilkie, D. P. D. 6	Brit. M. J., 1: 771, 1933.	249	29	11.6	Conservative.	Warns against operation in individuals "constitutionally inclined" to ulcer.

Christiansen, T. 10	Acta. med. Scandinav., 84: 374, 1934.	289	23	7.9	Starvation, then gradually increasing diet.	All massive hemorrhages. Transfusions have in- creased mortality. Mor- tality greater after 40 and in women.
Burger, G. and Hartfall, J. 10	Guy's Hosp. Rep., 84: 197, 1934.	137	31	22.6	Conservative, but some operated later.	Mortality 65% in operated cases. Three times as frequent in gastric cases.
Hellier, F. F., 7	Lancet, 2: 1271, 1934.	198	27	13.6	Nothing by mouth, then soft diet. Transfusions after 2nd hemorrhage.	Surgery only after 4 hem- orrhages, two-third deaths in those over 40 years of age.
Nitken, R. S., 5	Lancet, 1: 839, 1934.	234	20	8.5	Conservative for mild cases only; transfusions and surgery for severe ones.	Of severe cases, one third died. (See surgical group.)
Davies, L. and Nevin, R., 10	Brit. M. J., 2: 858, 1934.	385	79	20.5	Nothing by mouth; then soft diet. Transfusions in 37 cases.	50% mortality in severe cases.
Conybeare, J. J., 10	Proc. Roy. Soc. Med., 1: 228, 1934.	600	12+	2+	Type not stated.	Cases from Guy's Hospital from 1911 to 1920.
de la Viesca, P., 5	Arch. f. Verdauungskr., 58: 22, 1935.	130	9	6.6	Conservative.	Mortality 8 times greater after 40 years of age. Surgery for chronic in- durated ulcers.
Crossan, E. T.	Surg. Clin. N. A., 16: 461, 1936.	73	11	14	Conservative.	Advises operation only after conservative treat- ment fails.

TABLE 6 (Continued)

Author.	Years covered.	Reference.	No. of cases.	Deaths.		Treatment.	Comment.
				No.	%		
Hesser, S.	6	Acta med. Scandinav., (Supp.), 78: 409, 1936.	304	15	5	Conservative.	All severe cases; no deaths before 60 years.
Enocksson, B.	18	Acta med. Scandinav., Supp., 78: 415, 1936. (Discusses Hesser's paper.)	105	14	14	Conservative.	11 of deaths in those over 40 years.
Gram, H. C.	2	Acta med. Scandinav., Supp., 78: 423, 1936.	106	4	3.8	Meulengracht technic.	Some of fatal cases had complications not due to hemorrhage.
Goldman, L.	7	J. A. M. A., 107: 1537, 1936.	349	52	15	Nothing by mouth for 48 hours; transfusions. Operate when failure.	Mortality greater after second hemorrhage. All cases with gross hemorrhage.
Meulengracht, E.	6	Münch. med. Wchnschr., 84: 1565, 1937.	368	5	1.3	Full diet and iron from beginning.	Quick recovery from weakness and anemia.
Lineberry, E. D. and Issos, D. N.	7	South. M. J., 30: 1228, 1937.	36	0	0	Sippy regimen with sodium luminal intramuscularly.	Includes mild cases; one other case operated and died.
Witts, L. J.	2	Brit. M. J., 1: 847, 1937.	20	0	0	Meulengracht technic and large amounts of fluid.	Includes mild cases but all admitted for hemorrhage. Transfusions when pulse over 140, blood pressure under 90.

Stackford, J. M., Smith, A. L., and Affleck, D. H.	Am. J. Digest. Dis. and Nutrition, 4: 646, 1937.	36	6	18	Conservative.	All severe cases. Mortality 10 times greater after 50 years.
Hurst, A. F., and Ryle, J. A.	Lancet, 1: 1, 1937.	677	9	1.3	Conservative.	General practice.
		82	4	4.8	Conservative.	Guy's Hospital.
		258	14	5.4	Conservative.	Ryle's cases.
Boyd, L. J., and Schlachman, M.	Rev. Gastro-enterol., 5: 43, 1938.	30	6	20	Starvation and later conservative diet.	First series before June, 1937.
		15	0	0	Meulengracht.	Convalescence more rapid and pleasant.
Allen, T. G., and Bloom, K. A.	This report.	49	3	6.1	Conservative.	
		5843	508	8.7		
Totals						

The literature does not permit a definite statement as to the medical regimen instituted in all the other cases, but in most instances it resembled that outlined for our personal series: starvation and morphine throughout the period of active bleeding, then a diet resembling that of Sippy or Andresen for at least another week. Transfusions for the more severe cases were given by most of the authors, but Witts warns against transfusion unless the pulse rate exceeds 140, the blood pressure falls below 90 or the hemoglobin goes below 40 per cent. Allen also states that a transfusion should be given only when the systolic blood pressure reaches 70; he also avoids venoclysis, giving fluids by hypodermoclysis only. Goldman, whose mortality rate was 15 per cent, gives nothing by mouth until forty-eight hours after cessation of the hemorrhage and favors transfusions.

Thus some evidence seems to be available in the literature, from other authors, to support the contention of Andresen and of Meulengracht that the stomach should not be kept empty. Their dietary regimens, however, especially the more radical one of Meulengracht, deserve further trial, under carefully controlled conditions, before being accepted as routine methods of management.

A determination of the progress of the bleeding or of its cessation is obviously most important in the management of these cases. Our analyses have failed to reveal any helpful procedures, but the practice of applying constant slight suction on the stomach contents by means of a Levine tube introduced through the nose, and kept well above the usual ulcer-bearing area, deserves consideration. It tends to keep the stomach empty, which may not always be desirable, but at the same time it gives continuous objective evidence as to the presence and degree of active bleeding. Although this procedure was employed in some of our cases we did not allow it to influence us greatly in the decision as to the proper time for operation. We now believe, however, that it deserves attention in that respect.

A consideration of both of our own and the published data permits a few comments in summary. It is our opinion that at least 90 per cent of the cases can be successfully carried through their hemorrhage on a medical regimen. It may well

be that in this group a more liberal program of feeding should be adopted. They may subsequently be operated on, if necessary, without greater risk than in nonbleeding cases. It is the remaining 10 per cent that presents the serious problem in management. They are the ones that continue to bleed until death occurs or an open vessel is ligated. If operation is postponed in these cases we have seen that the operative mortality is appalling. The only hope of reducing the mortality is the early recognition that a given case belongs in this group, in which event prompt surgical treatment must be resorted to. The chief factors which have been taken to indicate that surgery is required are repeated hemorrhages and the advanced age of the patients. Our data, however, clearly indicate that fatalities are common in young individuals with no history of previous bleeding. We are, therefore, left without clear-cut indications for immediate surgery, and our decision must be based on a rather ill-defined and intangible clinical judgment, the limitations of which are apparent from the mortality statistics.

NOTE.—We are indebted to Drs. E. L. Eliason and I. S. Ravdin for placing at our disposal surgical records of some of the cases included in this report.

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THE DIAGNOSIS AND TREATMENT OF PAROXYSMAL CARDIAC DYSPNEA

THERE are few experiences more distressing or alarming than to awaken from sleep in a severe attack of paroxysmal cardiac dyspnea. A distinguished physician who had suffered this ordeal once told me that it was the worst experience of his life and that given his choice he would endure any pain rather than the almost intolerable shortness of breath.

The literature dealing with paroxysmal cardiac dyspnea is apt to give one the impression that all attacks are characteristically prolonged and severe. Nevertheless, in my experience minor attacks in which patients awaken with a sense of suffocation, sit up gasping for breath a few minutes, and then feel comfortable again, are far commoner than major attacks.

Patients do not always volunteer information regarding these minor nocturnal seizures in response to the questions usually asked about shortness of breath. A few years ago Dr. Francis Clark Wood and I became interested in the tolerance of cardiac patients for various positions of recumbency and began to question them in detail regarding the symptoms they experienced in bed. We were astonished to find how many suffered from minor attacks of paroxysmal nocturnal dyspnea even though the previously recorded history contained no reference to such events.

The question may be asked as to whether these minor seizures belong in the same category with the spectacular attacks which seriously threaten the patient's life. The evidence supporting this view is as follows: (1) All gradations of severity occur, from attacks so mild that the patient may quickly forget them up to those ending in death; (2) all gradations

tend to occur in patients with the same types of heart disease, in similar stages of their disease, and are apt to begin during sleep; (3) both major and minor seizures may occur at different times in the same patient although some who suffer from minor attacks do not develop major attacks; (4) those who have experienced both major and minor attacks usually regard them as of the same nature varying only in their severity.

The one symptom common to all attacks is shortness of breath. Some patients develop a loud wheezing or asthmatic type of breathing. Doubtless it was this feature which led Hope¹ to include this condition as a form of "cardiac asthma." The term as applied to these seizures has not proved so satisfactory as the purely descriptive designation of paroxysmal cardiac dyspnea. The fact that some patients during attacks fail to exhibit asthmatic type of breathing would make one hesitate to label such an attack "cardiac asthma." Thus the inexperienced physician may miss the true significance of the attack. On the other hand the occurrence of asthmatic type of breathing in a patient with heart disease or suspected of heart disease tempts the physician to call the condition cardiac asthma even though the asthma is not due to heart disease itself but is a manifestation of allergy. It is sometimes very difficult to decide whether asthmatic type of breathing is due to the cardiac difficulty or is allergic in origin. The differentiation is one of considerable practical importance since in the one case treatment must be directed mainly toward the heart and in the other toward the allergy.

The situation may change rapidly during an attack of paroxysmal cardiac dyspnea. If the patient does not begin to improve in from fifteen to thirty minutes, the chances are that he is heading for serious trouble. Cough, which is apt to come on promptly, becomes productive of frothy fluid which may be blood-tinged and profuse in amount. Examination of the lungs shows numerous crackling and bubbling râles and often sibilant râles and rhonchi. In the early stages of the attack, there is apt to be both tachycardia and elevation of the blood pressure. However, when the stage of acute pulmonary edema comes on, the blood pressure tends to fall and other evidences of circulatory collapse make their appearance. The patient exhibits a combination of pallor and cyanosis, he

sweats profusely, the pulse becomes extremely rapid and feeble, and the extremities cold. His condition is now extremely precarious and he may die suddenly. Some of these patients, however, make spectacular recoveries from what had seemed like hopeless situations.

Etiology.—The etiology of paroxysmal cardiac dyspnea has interested many students of heart disease; considerable thought and work have been devoted to the subject. The first requisite was to discover what types of conditions predispose to its occurrence. It was found to attack not only those either suffering from congestive heart failure or on the verge of heart failure, but occasionally individuals still able to work a full day without complaint. However, when we come to study these patients, it is found that all have one impairment in common, namely, some handicap to the movement of blood through the left side of the heart. The actual lesion is usually disease of the left ventricular myocardium (often following arterial hypertension, coronary arteriosclerosis, or aortic valve disease). Contrary to what has sometimes been stated in the literature, the condition also occurs in mitral stenosis, but the attacks which begin during sleep as a rule are not severe. Although paroxysmal cardiac dyspnea may occur in patients with weakness or disease of the right side of the heart, it is apparently not due to this impairment. There is some reason for believing that right-sided involvement has a tendency to protect the patient from attacks.

Why should patients with left-sided heart disease be subject to such violent attacks? Usually there is some obvious although not always entirely satisfactory explanation for the attacks which occur when the patient is up and about. They may follow overexertion, the inception of an abnormal cardiac mechanism such as auricular fibrillation, an attack of acute coronary occlusion, disturbances of the gastro-intestinal tract such as acute distention, or uncontrollable retching and vomiting. Any of these may suddenly handicap the left side of the heart and cause acute left-sided heart failure. However, the great majority of attacks begin when the patient is asleep and under conditions where none of the factors mentioned above is present. This remarkable fact has led to much speculation as to the precipitating cause or causes.

The following have received considerable attention as possible precipitating causes of paroxysmal dyspnea:

(1) *The Recumbent Posture*.—Harrison has emphasized this factor^{2a} and points out that some patients while asleep may slide down in bed to a position they are unable to tolerate. Fishberg³ agrees and regards attacks due to such a cause as essentially manifestations of orthopnea. However, it is recognized that such a mechanism cannot account for all attacks since some patients do not become dyspneic when recumbent if they remain awake, but may be aroused by shortness of breath if they fall asleep.

(2) *Sleep*.—It has been suggested that during sleep, diminution in the irritability of the central nervous system may allow pulmonary engorgement to attain a much higher degree before reflexly inciting an increase in ventilation than when the patient is awake. Thus the patient does not awaken until the lungs become intensely engorged. This explanation is open to question. While there is no doubt that an attack is apt to become well established before the patient awakens, there is reason to believe that increase in ventilation has already occurred. The history is occasionally obtained from the husband or wife that the breathing had become violent prior to awakening. The wife of a man I saw recently observed that he was wheezing and extremely short of breath, so she called to him and asked what was the matter. He replied that he felt all right, although apparently he did not awaken completely, and dropped off to sleep again. The violent breathing continued so she aroused him. He then began to cough and expectorate mucus and went through the typical course of an attack which did not abate for over two hours.

(3) *Periodic Breathing*.—According to this hypothesis, some attacks are inaugurated by the dyspneic phase of periodic breathing. Although patients often doze off during the period of apnea and then awaken suddenly during the dyspneic phase gasping for breath, I know of no cases in which an attack began in this way.

(4) *Dreams*.—In support of this view the oft-quoted observation of MacWilliam⁴ that during dreams both systolic and diastolic blood pressures may rise greatly, again does

service. One is justified in a reasonable amount of skepticism as to the importance of dreams in causing paroxysmal dyspnea.

(5) *Resorption of Edema*.—According to this idea, edema fluid resorbed from the tissues into the blood stream when the patient assumes the recumbent position, places a burden on the heart, which is tolerated by the right ventricle but not by the weakened left ventricle. This might possibly be a factor in certain patients who are up and about during the day but, as Fishberg points out, could scarcely account for the attacks of those who are in bed both day and night.

(6) *Cough*.—It is quite possible that a prolonged severe paroxysm of cough might initiate an attack, but there is little reason to believe that this is one of the important factors operating during sleep. As an etiologic agent it is akin to overexertion. So far as my experience goes, cough does not usually become a prominent feature until the attack is under way.

(7) *Reflex Factors*.—A number of authors have suggested that nervous reflexes from the lungs or aorta may be concerned in the initiation of attacks. Weiss and Robb⁵ believed that they were able to influence certain attacks by blocking the vagus nerve with procaine hydrochloride. The part played by nervous reflexes in initiating an attack is far from clear at the present time. Although the effect of nervous reflexes as the initial disturbance in the chain of events leading to an attack of paroxysmal cardiac dyspnea may be questioned, there is every reason to believe that they play an important part in the production of the dyspnea itself. Such an effect, however, may be secondary and due to engorgement of the lungs with blood.

(8) *Cerebral Factors*.—The discussions of this possible factor center mainly about the assumption that diminished cerebral blood flow occurs as a result of cardiac failure, causing an inadequate interchange of gases between the blood and respiratory center. This in turn causes disturbances in respiration leading to paroxysmal dyspnea.

(9) *Chemical Factors*.—Some writers have assumed that insufficient aeration of the blood and accumulation of carbon dioxide or other acid metabolites during sleep may be responsible for attacks. This hypothesis is closely related to the pre-

ceding one. Harrison,^{2b} however, states that he was unable to find alterations in hydrogen ion concentration, carbon dioxide, or oxygen content of the blood to support such an hypothesis.

There can be little doubt that in certain instances orthopnea is related to paroxysmal cardiac dyspnea. Brief attacks of severe dyspnea may be produced in orthopneic patients by having them lie in a horizontal position until they become uncomfortable. It seems reasonable to believe, as suggested by Harrison and by Fishberg, that some attacks of paroxysmal cardiac dyspnea may be produced by patients sliding during sleep to a position lower than they are able to tolerate. It is of interest, however, that the level at which a patient lies is not the whole story. Some who are intensely orthopneic while in the supine position, are able to lie prone in comfort.

When Wood and I began to study the tolerance of cardiac patients to various recumbent positions,⁶ it soon became obvious that there was a close relationship between orthopnea and trepopnea.* Although trepopnea may appear in a patient a long time before orthopnea, it seemed to us probable that both were manifestations of the same underlying mechanism for the following reasons: (1) The symptoms produced by assuming an unfavorable recumbent position are the same as those experienced by an orthopneic patient when he lies flat in bed, namely, dyspnea and precordial oppression; (2) both orthopnea and trepopnea may change as cardiac failure appears and disappears; (3) these two phenomena are seen in the same general group of patients; (4) they are frequently seen combined in one patient, *i. e.*, an individual, if uncomfortable lying flat on his back or on the left side, may be able to achieve comfort by sitting up or remaining flat and rolling to some other recumbent position.

After having satisfied ourselves as to the close relationship between orthopnea and trepopnea and having studied the mechanism of trepopnea so far as we were able, an attempt was made to find out the relationships of trepopnea to nocturnal paroxysmal cardiac dyspnea.⁷ We found only a small percentage of patients subject to paroxysmal nocturnal dysp-

*Trepopnea is a term which we have used to denote the condition in which a patient may develop such symptoms as shortness of breath or precordial distress in one recumbent position and not in another.

nea, who did not have definitely demonstrable trepopnea, and 2 out of 4 such patients stated that their attacks of dyspnea occurred only when they lay on the left side. However, it should be stated that there were a few patients with both paroxysmal nocturnal dyspnea and trepopnea who did not recognize an etiological relationship between the assumption of the unfavorable recumbent position and their nocturnal attacks. Whether observations on the beginnings of attacks in these patients would have shown a relationship has not been established. However, in a considerable group of patients, the evidence pointed strongly to a relationship between trepopnea and paroxysmal dyspnea. In 1 case of this group the patient's wife had recognized this relationship before we saw him. Whenever she was awakened by her husband "panting" heavily, he would be found lying on his left side. If he were not disturbed he would develop a severe attack of paroxysmal dyspnea. If, however, she rolled him over to the right side the "panting" would cease whether or not he was awakened in the process. In another case it was possible to provoke an attack of paroxysmal dyspnea lasting several minutes by rolling the patient while he was asleep onto his left side.

These observations left no doubt in our minds that trepopnea including orthopnea is concerned in the production of many attacks of paroxysmal nocturnal dyspnea. The evidence we were able to obtain, points to the view that the symptoms of trepopnea are due to the fact that, in unfavorable positions the flow of blood from the lungs to the left side of the heart is retarded, possibly by pressure on pulmonary veins. Thus in a patient already handicapped by heart disease, the imposition of another handicap may be more than the left side of the heart can tolerate. Pulmonary engorgement begins and initiates the train of symptoms.

Early in our study we encountered two findings which seemed at variance with the idea that trepopnea was an important factor in the production of paroxysmal dyspnea. The first of these was the fact that many patients with trepopnea do not have attacks of paroxysmal dyspnea. Study of these patients showed that: (a) some with mild trepopnea are able to sleep in unfavorable positions without difficulty, (b) some patients seem to be able to avoid their unfavorable positions

without waking, and (c) most of these patients do awaken when they get in an unfavorable position, but dyspnea may be mild or absent. These patients may awaken with: (1) pain, either anginal or more often nonanginal; (2) a combination of pain and dyspnea; (3) palpitation; (4) cough; (5) indefinite disagreeable sensations, and (6) bad dreams. The second finding that did not seem to fit in with the relationship between trepopnea and paroxysmal dyspnea was the fact that trepopnea was a common finding in patients with mitral stenosis and auricular fibrillation, whereas paroxysmal dyspnea is reported as uncommon in either of these conditions. Nevertheless patients with mitral stenosis or auricular fibrillation are frequently awakened at night by cardiac symptoms such as palpitation or precordial distress. Such symptoms may actually be beneficial in that they do not permit the seizure to progress to the point of severe dyspnea. Likewise patients with extreme congestive failure and severe trepopnea usually awaken promptly before a major attack of dyspnea is under way. It seems therefore that a patient must be able to endure sleeping in his most unfavorable position for a considerable period in order to bring on a severe prolonged paroxysm of dyspnea.

The recognition of trepopnea as a factor in the production of paroxysmal cardiac dyspnea during sleep has removed some of the mystery from the etiology of this condition. Persistence in an unfavorable recumbent position seems capable of bringing about pulmonary engorgement in a patient with impairment in function of the left side of the heart, quite as surely as overexertion. The course of events from then on depends on the ability of the heart to cope with the burden of pulmonary engorgement.

Treatment.—The treatment of paroxysmal cardiac dyspnea, like that of other paroxysmal cardiac seizures, falls into two categories, namely, preventive measures and treatment of the attack itself. The two should not be confused since they are totally different. In preventive treatment the individual must be carefully studied with a view to instituting any type of treatment that may help sustain his circulation. In this connection one may have to treat such diverse conditions as anemia, allergy, obesity, diabetes mellitus or prostatic obstruc-

tion. Attention should be paid to all aspects of the regimen of life, to ease the burden on the heart. The great majority of patients who are subject to paroxysmal dyspnea should receive a daily ration of digitalis but the dosage should be kept below the level of toxic symptoms. It should be used very cautiously in those who have suffered recent coronary occlusion and those with minor grades of heart block. A single dose of one of the theophylline compounds just before going to bed may be helpful. I do not favor heavy dosage of barbiturates. If sleep becomes too profound the patient may not awaken until an attack has reached the dangerous stage. If the patient has definite orthopnea or trepopnea, an effort should be made to help him avoid unfavorable positions. Dr. Francis Clark Wood has suggested the use of a fairly tightly fitting jersey with spools sewn in such places that the patient will awaken promptly when he rolls into an unfavorable position.

In the treatment of an attack, speed is of vital importance. The physician who is summoned to such a case should waste no more time than a fireman going to a fire. When called and told that the patient is having a severe attack of shortness of breath he should instruct the family to keep him upright, but covered with blankets, open the windows, give him hot strong coffee and whisky or brandy and a tablespoonful of paregoric. When the doctor arrives, the first decision he has to make is whether to use a hypodermic injection of morphine. This decision is usually easy. If the patient has not obviously improved, he should receive it immediately. Morphine is the sovereign remedy for the treatment of paroxysmal dyspnea. The mechanism of its beneficial effect is not understood entirely, although many believe that the quieting of respiration and the consequent lessening of pumping action favoring venous return to the right side of the heart is the important action. If the first injection of morphine does not begin to give relief in fifteen minutes, a second should be given.

There is some difference of opinion as to whether atropine should be given with the morphine. The main objection advanced against its use has been that atropine may increase the heart rate and therefore have an unfavorable effect. While there is no question that atropine in sufficient dosage is capable

of accelerating the normal heart rate, I have not noted such an effect when atropine was given with morphine during an attack of severe paroxysmal dyspnea. Some who favor the use of atropine do so on the ground that it retards the accumulation of fluid in the lungs, analogous to certain of its effects on secretion. However, there seems to be little more justification for believing that atropine will check pulmonary engorgement and passage of fluid from the vessels than for believing it would retard the formation of edema of the legs. I have not used atropine alone without morphine but have not observed that patients receiving both drugs do better than those receiving only morphine.

Recently solutions of theophylline compounds given intravenously have become quite popular in the treatment of paroxysmal dyspnea. There is no doubt that theophylline given in this way is a highly effective remedy. One of our patients who has received morphine hypodermically in some attacks and theophylline intravenously in others, prefers the theophylline on the ground that it gives more prompt and complete relief. This patient, however, is one in whom asthmatic type breathing during attacks is a prominent feature, so that the prompt relief from theophylline in his case may be due to its spectacular effect on bronchial spasm. It seems to be beneficial also in cases without asthmatic type breathing. I have never observed untoward effects from the use of theophylline given intravenously, beyond a transitory sensation of discomfort in the chest. However, I saw in consultation a woman in a distressing attack of bronchial asthma which was not relieved by large doses of adrenalin and morphine. An intravenous injection of theophylline began to give relief within ten minutes and in thirty minutes she was comfortable. A few days later, her physician reported to me that she had another attack and that following another intravenous injection given quite as slowly as the first, she collapsed and almost died. Although not too much stress should be placed on a single episode of this type, I believe that further experience with the intravenous use of theophylline is required before its use is to be recommended without reservation in mild seizures which do not threaten life. However, in serious attacks, I

believe it should be used promptly, if morphine has not brought about improvement.

I have long regarded caffeine and epinephrine as useful drugs in the treatment of paroxysmal dyspnea but the theophylline is so much more effective that we find ourselves using less and less of these two. However, if theophylline is not immediately available, they may be used. Epinephrine, however, should not be given to patients suspected of having coronary disease.

I find that many physicians in treating attacks of paroxysmal cardiac dyspnea are apt to give hypodermic injections of digitalis. The dosage usually employed ranges from $1\frac{1}{2}$ to 3 grains. Although, as stated above, digitalis is often useful as a preventive measure it must be given in therapeutically effective dosage. I object to its use during an attack for the following reasons: (1) The dosage is usually too small to be effective; (2) even though enough be given, its action is too slow to combat an emergency, and (3) the use of digitalis may divert attention from more effective measures that should be employed.

Venesection, with the rapid removal of at least 500 cc. of blood, is undoubtedly a beneficial procedure in many patients with paroxysmal dyspnea. It is unfortunate that we have so little accurate knowledge regarding the mechanism of its action in various types of disturbances of the circulation. There is good reason to believe that the level of venous pressure has much to do not only with ventricular filling but ventricular contraction as well. Thus venesection by lessening venous pressure temporarily may decrease the output from the right side of the heart and in this way lessen the burden on the lungs. The application of tourniquets to the extremities just tight enough to obstruct venous return but not arterial flow, may also be helpful.

When oxygen therapy is available it should be instituted as promptly as possible and continued until the danger has passed. Unfortunately many attacks occur in places where oxygen is not available during the immediate crisis.

After the acute emergency has passed, the treatment must depend on the circumstances of the case. The man who has had a major attack of paroxysmal cardiac dyspnea may never

again be as well as he was before and his tenure of life becomes as uncertain as that of the victim of acute coronary occlusion. The heart muscle cannot be relied upon thereafter. The duration of life depends on a variety of factors as is always the case in chronic heart disease. One of the most important of these is the measure of success in preventing or aborting further attacks since every one is a menace.

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CLINIC OF DRS. EDWARD A. STRECKER AND
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THE MODERN TREATMENT OF SCHIZOPHRENIA
(DEMENTIA PRAECOX)

We have attempted to give you a clinical and psychological appreciation of schizophrenia, which is unquestionably the gravest disease threat of our civilization.

It would appear that the outstanding characteristic of schizophrenic patients is that they tend to live in a world of their own. Practically all of the clinical symptoms are reducible to this phenomenon of psychological isolation. The "splitting" of the mind from which the psychosis derives its name is a lack of unity and parallelism between thought content and emotional accompaniment and it imparts an extremely bizarre expression to schizophrenia, setting it apart from all other behavior reactions, normal or psychotic.

From the standpoint of therapy there are at least four important considerations: First, with the much better understanding of the particular type of introverted personality soil in which the psychosis so readily takes root, there is now a much better opportunity for the exercise of preventive measures during childhood. Second, schizophrenia is not only extremely common, but it makes its appearance in about 70 per cent of the patients during the second decade of life. Therefore, effective treatment is unusually important. Third, the chances of successful therapeutic results diminish rapidly as the duration of the psychosis increases. Fourth, prognostic considerations have been greatly improved by modern pharmacological methods and technics.

Preventive Measures.—Prophylaxis must be intensively cultivated during childhood and every child who presents

schizoid characteristics ("good," "quiet," "shy," "reserved," "difficult," "unsociable," "seclusive," etc.) should be the target for intensive prophylaxis. The objective is to attain a better balance between child and environment and, in some sense, to promote socialization.

For the child, the home should be first and foremost a place in which there is an atmosphere of harmony and happiness. There should be neither unduly harsh discipline, nor its opposite, spoiling. Competition between brothers and sisters in the home for the favor of the parents, particularly when spurred on by "playing favorites" by the parents, is pernicious. The attempt to stimulate a child by too constantly pointing out the assets in brothers and sisters usually results in the production of inferiority feelings and is a hazardous process. There should be liberal doses of explanation to the child in the parent-child relationship and particularly should punishment contain a generous leaven of explanation. Companionship with other children of both sexes, outdoors, athletics, and all reasonable socializing influences should be encouraged. It should be made easy for the child to bring his playmates into the home and there should be no risk that things would be seen or heard there that would shame him before other children. Sex and particularly the concrete facts of sex are always difficult for the potential schizophrenic and "therefore effort should be made to prevent phantasy by supplying competent knowledge of sex hygiene, and to discourage rumination by always discussing such matters without emotion and with only a modicum of moralization." Sex instruction should be begun comparatively early in childhood, but naturally in a degree and in detail suitable to the age of the child.

Children have toward their parents an attitude of idealistic identification. Unconsciously, they supplement their own weakness by identifying themselves in the parents. Here is a strong emotional bond, leading to indiscriminate imitation and containing sources of danger, particularly for the introverted child. The goal of any real psychology of childhood is to obtain for the child a true psychological maturity. If this is not accomplished, the child is destined for a life of slavish imitation of those who become the emotional surrogates for his parents. The parent-child bond must be loosened not too

abruptly but nevertheless surely, and independence of thought and action must be wisely and continuously encouraged.

Introverted children read a great deal and while their reading should not be too rigidly ordered yet, it should be directed toward types of literature that are not too luridly and completely phantastic. Religion supplies an important need and it should be a source of beauty and inspiration but social and practical too, and above all not grimly fear-producing.

"The schooling of these children should be carefully scanned and means found to check the tendency to study abstruse and obscure subjects. Rather should socializing subjects be emphasized, that youth may keep close to facts and maintain friendly personal contacts. Primacy in competition of intellects is a goal to be disparaged . . . the choice and any change of occupation should be given consideration by those interested in order to prevent the development of illness; and any inclination to choose a vocation that merely promises compensation for ill-recognized inferiority feelings should be skillfully handled. The vocation selected should be certainly within the capacity of the individual and of a type to maintain his social life on as broad a scale as may be within his power." (Hamilton.)

Treatment of the Psychosis.—Obviously the earlier the actual schizophrenia is treated correctly, the better the chance of adjustment. In combating schizophrenia the psychiatrist needs the inspiration of a workable conception. We know of no better conception than the psychobiological interpretation of Meyer. It views the patient critically in the long section of his life history and particularly surveys the series of maladaptations that preceded the final schizophrenic one. It then asks such pertinent and therapeutically stimulating questions as these: What are the resources of the patient? What has he to react with? What is the situation he is called on to meet? Can we modify his resources in order to enable him better to meet the situation, or can we modify the situation so he may better meet it with his resources? Etc. Finally, the psychobiological idea does not court exclusively any single therapeutic mistress and it leaves open the door of every reasonable treatment plan.

Psychotherapy.—There are many kinds of psychotherapy

and we believe the more individualistic the approach the better. Generally speaking the psychiatrist will find his patient living on the plane of unreality or dangerously close to it. Between this and the reality which is possible for the patient and which varies for each patient there is a gulf which must be bridged if adjustment is to be secured. The steps between phantasy and reality cannot be forced too abruptly but must be taken, psychologically speaking, slowly and gradually. The building up of confidence, persuasion, suggestion, particularly the indirect suggestion that skilfully and not too obviously puts forth the claims of reality, are helpful. All this implies some degree of accessibility on the part of the patient but so is this a requisite for any form of psychotherapy and in the bulk of early cases some degree of accessibility is at hand. Once a bit of insight is secured and there is some beginning of the process of viewing the symptoms objectively, then this advantage should be pressed and expanded.

There is much difference of opinion concerning that specialized form of psychotherapy known as psychoanalysis. Some authorities feel that dangerous panics result from the inability of the patient to face the probable incestuous significance of the phantasies, and that the physician becomes a part of the phantasy. Others think that this is merely a difficult place in the treatment plan and that it can be won through. It is obvious that in any event psychoanalysis must be modified if it is to be used in the treatment of the schizophrenic.

General Management.—In well-established schizophrenia the majority of the patients must be treated in suitable mental hospitals or sanatoria. In this way the medical interests of the patient, his safety, the safety of the community and the welfare and efficiency of the family are best protected and conserved. Under skilful supervision and, if satisfactory conditions are available, a number of patients may be cared for in the home, particularly during the "quiet" periods of the psychosis. In some instances farm or ranch life is a good solution. In early or mild cases, the out-patient clinic or private physician can satisfactorily direct the care of the patient in the home. The placement of the patient in suitable homes and the community plan as it is followed at Gheel,

Belgium, deserve wider recognition. Whether the patient be in hospital or at home, adequate nursing, occupational therapy and proper social service are important. The nurse is the representative of the psychiatrist and, if well trained, she will know how to attempt to check the inroads of phantasy and how to set forth in theory and practice the claims and advantages of reality. The social service worker if not too fanciful is especially valuable in the "follow-up" of adjusted patients and in the instances where patients are kept in the home, she should combat the danger of family disorganization. Occupational therapy is an extremely valuable and a necessary treatment adjunct. It is constantly symbolic of reality rather attractively garbed, and it produces the concrete fruits of work.

Treatment of Special Symptoms.—The good nurse will know how necessary it is to see that the patient has sufficient nourishment; that he is tube fed when necessary; that he is kept clean, bathed frequently, changed when he wets or soils himself; that dangerous and sharp objects with which the patient might mutilate himself or others are not available; that the patient has enough exercise, sunshine and fresh air; that the chronic patient is taught useful habits and some routine, at least, in the care of the bodily functions and the nurse, too, will minimize and control the physical dilapidation of appearance which is such an early result of the shutting out of reality. The prolonged bath, wet packs, etc., sometimes quiet the excited states. Apathy must be often the target of special measures: walks, calisthenics, physical culture, apparatus, athletic games, indoor games, cards, other diversions, garden work, motion pictures, and the theatre, music, dancing, garden work, arts and crafts especially basketry and weaving, etc., are all helpful. Sometimes in stupor visiting by relatives is beneficial.

Pharmacological Therapy.—Until comparatively recently the treatment which has been outlined constituted the extent of our therapeutic resources. A therapeutic renaissance has appeared, which boldly and rather successfully attempts to strike directly at certain chemical factors which may be causal of schizophrenia, or which, at least, may provide conditions under which the psychosis becomes chronic.

NEWER FORMS OF THERAPY IN SCHIZOPHRENIA

Insulin.—Among the newer forms of therapy in use in schizophrenia insulin shock therapy and treatment with metrazol rank first in importance. The present form of insulin shock therapy was first used by Manfred Sakel of the Wagner-Jauregg Clinic in Vienna, and to him goes the credit for having discovered it. While Sakel was the first actually to use hypoglycemic shock in the treatment of schizophrenia he was not the first to use insulin in the treatment of psychotic patients. Other investigators had tried it as a means of increasing the appetite and promoting nutrition in mental patients. As early as 1928, Haack in Germany had reported improvement in the mental status of patients being treated with insulin. Steck in Switzerland reported the same results but both men buffered the injection and warned against hypoglycemia. In America, Appel, Farr and Marshall of the Pennsylvania Hospital began work with insulin in 1928 and 1929 as did Strecker and Palmer. The first mentioned group gave up to 70 units a day in an attempt to improve the patient's nutrition. They noted improvement in one patient who had a hypoglycemic reaction but did not follow it through. Therefore Sakel fathered the present type of treatment and was the first to devise a safe technic and elaborate a successful method of treatment on that basis. He announced the results of his five years' observation at a meeting of the Vienna Medical Society in November of 1933. He reported that 58 patients who had been ill six months or less had been under treatment and that 70.7 per cent responded with a full remission and a further 17.3 per cent responded with a good social remission, a total of 88 per cent positive results. His reports were soon confirmed by Max Müller of Munsing Hospital in Bern, Switzerland, who reported that out of 136 patients who had been ill less than six months 89 per cent had improved, 73 per cent being full remissions. Among those patients whose illness had lasted six to eighteen months 82 per cent were improved, 50 per cent being full remissions. A third major series of cases was reported from Yugoslavia in November of 1936 and the investigators noted 70.58 per cent remissions but there was 1 fatality.

In America, credit for precedence in the actual beginning of insulin shock therapy no doubt goes to Cameron and Hoskins of the Worcester State Hospital. Glueck's glowing account of his visits to Munsing and Vienna was published in September of 1936 and stimulated great interest in the work in this country. Wortis had been active with the treatment in Bellevue Hospital in New York and very soon the therapy was begun in the Pennsylvania Hospital, Philadelphia General Hospital, and in many of the larger clinics of the United States.

It was apparent that any form of therapy which showed such excellent results in a psychosis which had had such poor prognosis would attract a great deal of attention. Bond and Braceland had reported in a five-year follow-up study that only 11 per cent of all patients who had been treated and then followed for five years had shown good remissions. This included the cases in which the remissions were spontaneous and those which were brought about by any type of therapy. The disparity between the recoveries reported is apparent. If the new figures were to be really correct, a great deal of good would be expected from this type of therapy.

Essentially the treatment consists of the production of consecutive daily insulin shocks. This is accomplished with the injection of graded doses of insulin, usually starting with 20 or 30 units or less and increased by 5 or 10 units until the shock dose is reached. The insulin usually produces somnolence and coma accompanied by profuse perspiration, giving a clinical picture which was formerly regarded as being alarming. Sakel calls these "wet shocks." Occasionally a severe epileptiform seizure is produced and he calls this "dry shock." Sakel divides the treatment into four phases:

1. Preparatory or introductory.
2. Shock phase.
3. Rest phase.
4. Transitional, polarization, or terminal stage.

The first stage simply consists in the preparation of the patient for shock. Few symptoms are seen. The patient's skin is usually moist and he may complain of hunger. As the dosage increases the patient shows more severe symptoms; he may become quiet, perspire profusely, exhibit forced blinking,

twitching of the lips and facial muscles and drowsiness progressing to stupor. When this stuporous stage progresses to coma the preparatory stage is at an end and the patient is regarded as being in the shock phase.

Typically, the shock starts with profuse perspiration, proceeds with increasing somnolence and finally goes over into coma. It might be interrupted temporarily by psychotic excitement. The patient is in true coma when he does not respond to stimulus. Sakel uses the loss of the swallowing reflex as the criterion of coma. There is usually drooling from the corners of the mouth. The pupils are small at the onset of coma and dilate as it deepens. It has been found that once the shock dose is reached and is established, invariably it is possible to lower the dosage and yet produce coma. The patient may show minor twitches, that is, transient perioral or periorbital twitches which are not rhythmic. There is no cause for alarm in these minor twitches; they simply indicate that the patient is going into coma. The patient recovers from them spontaneously. During this stage no stimulus of any kind should be permitted lest perhaps it bring on major twitches. Major twitches are characterized by a rhythmic clonic jerking involving facial and somatic musculature. If allowed to progress these major twitches increase in both frequency and severity until they approximate a clonic convulsion. The stage in which the twitches are present is sometimes called "restless stupor." Either restless or quiet stupor usually precedes the coma. As the hypoglycemia deepens the pulse usually becomes slower. Respiration deepens but the rate increases slightly. The temperature drops. Perhaps the most difficult thing of all is to decide when the opportune time has arrived to interrupt. As Sakel says the therapeutic effect does not depend on the amount of insulin or on the duration or depth of the coma. It depends on the accurately timed moment of interruption of the hypoglycemic state. Experience is the essential factor here and there are no known criteria which direct one when the hypoglycemic state should be terminated. The shock phase is interrupted by sugar solution given through a nasal tube or by an intravenous injection of glucose. Intravenous glucose is of course used in any case of emergency. The immediate period following the interrup-

tion is a time of mental clarity and alertness. At first this period is of relatively short duration but the time lengthens as treatment proceeds. Late in the treatment in those patients who are improved the psychotic symptoms are removed and the normal personality can again achieve complete dominance.

Sakel believed that in schizophrenia the cortical cells were continuously exposed to an adrenalin-like substance and that insulin was its antagonist. He therefore felt that the effectiveness of hypoglycemic treatment was due to the action by insulin directly on the cell itself. He assumed that the products of the adrenalin substance sensitized the cells excessively so that normal adequate stimuli produced pathological effects. Insulin opposes the action of the products of the adrenalin substance so that excessive stimuli are muffled and the cells kept relatively quiescent with benefit to the individual. He believes that this occurs in phase 1. Sakel continues that this stimulating hormone not only stimulates the activity of the individual cell but also revives forgotten phylogenetically ancient and infantile nerve pathway patterns which are normally latent and subdued in healthy waking thought. In the pathologic conditions were described all of these old patterns and called into action again they interfere with each other and produce what Stransky calls "intrapyschic ataxia." The nerve pathway patterns are shattered by phase 2 which is the shock phase and the normal pathways take precedence. In the convalescent period he feels that pathological nerve pathways remain subdued and the normal pathways remain inactive. In the last phase the normal cellular relations are reinforced by further injections and are said to be polarized.

At present the Pennsylvania Hospital statistics show the following. Seventy-two cases have been treated. At the end of treatment 45 per cent showed either clinical or social recovery. Within a period of weeks or months 15 per cent had relapsed, giving us a present recovery rate of 30 per cent. These statistics are at marked variance with the high recovery rates reported on the continent. One of the reasons for this disparity is probably that 15 of our cases were chronic and of long standing, a few of the 15 having been here for fifteen years. We are able to agree that the newer the patient's ill-

ness, the more hopeful the prognosis under insulin therapy. It is interesting to note that in a recent review of the cases done in the State Psychiatric Institute of New York they reported 58 patients treated. Out of the first 47 it was found that 26 per cent had recovered, 17 per cent were much improved, and 17 per cent were improved. Apparently the paranoid patients do better under insulin than do other types of schizophrenia. No doubt as the number of cases treated increases the recovery rate will average about 35 or 40 per cent.

We should mention that due to the rigors of insulin therapy any gross lesion especially of the cardiovascular system should be considered a barrier to the initiation of treatment. The older the patient the more care must be taken in gauging the dosage and in carrying out the technic.

Metrazol.—Ladislaus von Meduna of the Royal Hungarian Hospital in Budapest was the first to utilize metrazol for the treatment of schizophrenia. In July of 1935 he reported the results of his experiments with convulsive agents. The idea of treating schizophrenics by inducing convulsive states was based upon observations by Nyiro and Jablonszky, G. Müller, A. Glaus and others who had studied the few cases of schizophrenia which were accompanied by epilepsy. They concluded that epilepsy militated against the development of schizophrenia and on the basis of these observations formulated the following hypothesis:

“Between schizophrenia and epilepsy there is a biological antagonism. Should it be possible to induce epileptic attacks in schizophrenic patients, such epileptic attacks would change the chemical, humoral, haematological and other aspects of the organism in such a manner that thereby—since the organism so changed would represent an unfavorable basis for the development of schizophrenia—a biological possibility is given for a remission of the disease.”

They experimented with several convulsants. Camphor was more successful than the others but they found they were unable to fix the dosage. Metrazol was selected as it was more consistent in its action and readily soluble in water. Also, it is absorbed completely and rapidly even in large doses and it has no injurious effect upon the heart. Von Meduna started to treat schizophrenic patients with this drug; he began

by injecting 5 cc. of a 10 per cent solution into the veins. As a rule, there was a convulsive attack immediately after the injection. As long as the amount sufficed and a convulsion resulted the dosage was not increased. After the patient developed a tolerance, however, the dosage was increased by 1 cc. of a 10 per cent solution daily until in some cases as much as 15 cc. was given. Von Meduna treated the patients twice weekly. Other investigators, notably Friedman in America, treated the patients every second day. The number of treatments vary with the investigator, usually averaging 2 or 3 weekly.

At first the convulsion is tonic in character but within a few seconds it becomes clonic. The convulsions simulate epilepsy including the aura and automatisms. Before the onset of the convulsion there is always a tonic yawning movement which allows insertion of the gauze pad to protect the patient's mouth. During this latter phase the patients often urinate, the pupils are dilated and do not react to light and there is a positive Babinski. As mentioned before, it simulates an epileptic attack. After the attack, the patients in most cases are confused and dizzy and fall into a deep coma-like sleep which lasts from five to ten minutes. They again regain consciousness but are quite exhausted and fall asleep again and five to six hours after the attack they are allowed to take nourishment and move around. No definite number of convulsive seizures has been fixed as the curative number. In some cases the patients were better after 2 or 3 attacks; other required 25 treatments. As a general rule 15 attacks are induced even in patients who are not improving. If the patient has had an apparent remission it is well to give 3 or more convulsions despite this. Von Meduna pointed out that the blood picture changes under metrazol therapy. The lymphocytes are reduced and the neutrophils are increased. This was particularly so in patients who showed a remission. Also, the urinary acidity is increased about 25 per cent while the phosphates are increased 10 per cent. The chlorides are decreased 25 per cent. The investigators called our attention to the fact that in epilepsy these findings have been observed by various authors. Even though the attack seems to be appalling, the workers feel that there is no inherent danger in this type of

treatment. Several thousand convulsions have been induced without any serious complications. Dislocation of the jaw has occurred and occasionally a dislocation of the shoulder.

In von Meduna's report he chronicles the results of treatments in 110 patients, of whom 54 had a remission. This is roughly about 50 per cent. As stated above, the remissions in patients untreated range around 11 to 15 per cent. If we were to take the patients who were ill less than one year, von Meduna's figures would show a remission as high as 90 per cent. Von Meduna's experiments have been corroborated by many other investigators. In America, Finkelman, Steinberg and Liebert of Elgin, Illinois, reported on the treatment of 66 patients with dementia praecox by the administration of metrazol. They reported that 85 per cent of the patients whose symptoms were less than six months in duration had a remission. The rate of remission, they felt, was invariably proportionate to the duration of the psychosis. They say that if the psychosis has lasted more than three years, the anticipation of a remission is slight. Patients who had been ill longer than eighteen months required larger doses of metrazol and more treatments.

The type of dementia praecox that has the greatest tendency to remit with this therapy is the catatonic followed closely by the paranoid. It will be remembered that the paranoid type responds best to insulin shock. The following contraindications to metrazol therapy are listed: Failing or decompensating cardiovascular system, acute infectious diseases, and pulmonary diseases. Other investigators claim that severe anemia or cachexia, menstruation, history of cranial injury with subsequent unconsciousness should be added to the list of contraindications. The rate of injection of the metrazol is also important. It should be given at the rate of 0.1 cc. every ten seconds. The same dose of the drug given rapidly will produce convulsions which will not occur if the injection is given slowly. Wahlmann in Germany remarks that in hebephrenic cases it is difficult to judge improvement, but 3 of these patients were apparently improved and discharged from the hospital and at the time of writing had not returned. He also noted that the patients who reacted more severely to metrazol showed a greater degree of improvement, that is, that im-

provement seemed to depend directly on the degree of convulsions produced.

In recent literature we find that von Meduna and Sakel both claim credit for priority in the use of convulsions in the treatment of schizophrenia. Von Meduna points out that Sakel very carefully avoided allowing his patients to go into convulsions and that other investigators warned about it also. Sakel contends that he also used camphor and metrazol to provoke epileptic convulsions as far back as 1933. Sakel says his article was written in order to avoid an unfavorable schism in the pharmacological shock therapy. Ziskind reviews some of this quarrel and says that Sakel regards convulsions in insulin therapy as "heavy artillery" and prefers to use "light artillery" even though he recognizes that favorable effects sometimes follows major seizures. He points out that according to Grayzel convulsive paroxysms in rabbits cause cerebral damage. When no convulsions followed the insulin injections there were no microscopic pathological changes in the brain; after slight convulsions there were minimal changes; after one or more severe convulsions there were definite anatomic lesions. The greater the number and the more prolonged the convulsions the more severe were the lesions and among other changes there were small zones of focal necrosis in the cerebral cortex. The dose of insulin was comparable to that used in schizophrenia. Individual reactions with insulin should preferably be avoided. Ziskind remarks: "What bearing these histopathologic observations have on convulsant therapy with camphor or Metrazol can only be a matter of conjecture. The question is worthy of further study."

While we have been using metrazol therapy in the treatment of dementia praecox, as yet we do not have a sufficient number of cases to speak with any authority.

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TOXIC AND INFECTIOUS JAUNDICE

ONE of the most interesting and at times one of the most puzzling problems confronting the practitioner is the jaundiced patient. In this discussion, an attempt will be made to evaluate the etiology, differential diagnosis and treatment of the various forms of toxic and infectious jaundice. The following classification is presented merely as a matter of reference for the physician. No classification of jaundice can be perfect as several varieties are frequently combined.

CAUSES OF JAUNDICE ^{12, 26, 35}

I. OBSTRUCTION OF THE BILIARY DUCTS

- (A) Calculi, inflammatory exudates, parasites, neoplasms, etc.
- (B) Congenital stenosis, stricture from chronic cholangitis, etc.
- (C) Pressure from enlarged lymph nodes, abscesses, gumma, tubercles, echinococcus cysts, aneurysm of the hepatic artery, peritoneal adhesions, tumors of the pancreas, gallbladder and liver, etc.

II. TOXIC AND INFECTIOUS

- (A) *Chemical poisons*: Chloroform, carbon tetrachloride, cinchophen, gold salts, arsphenamine, neoarsphenamine, sulfarsphenamine, silver arsphenamine, stovarsol, phenobarbital, dinitrophenol, yatren (iodoxyquinoline sulfonic acid), dimethyl nitrosamine, arsenietted hydrogen, ethylene dichloride, tetrachlorethylene, trichlorethylene, tribromomethyl alcohol (avertin), ethyl chloride, ethyl bromide, compounds of antimony, manganese, cobalt, lead, copper, thorium, urea-stibamine, plasmoquin, acriflavine, dinitrobenzene, trinitrotoluene, trinitrophenol (picric acid), phenylenediamin, Bayer 205, rotenone or tubotoxin (an insecticide and arrow poison), impurities in alcohol, tar products, phosphorus, mushroom poisoning.
- (B) *Diseases*: Acute catarrhal jaundice, cholangitis, epidemic jaundice, infective hepatitis, yellow fever, syphilis, Weil's disease, toxemias of pregnancy, acute acidosis, typhoid and paratyphoid fevers,

dysentery, food poisoning, relapsing fever, dengue, Rift Valley fever, gonorrheal perihepatitis, Dourmashkin's syndrome, kala-azar (?), acute yellow atrophy (acute necrosis of the liver), Laennec's cirrhosis, prolonged anoxemia from chronic venous congestion with cardiac lesions (including coronary artery occlusion), lobar pneumonia, septicemias, Oroya Valley fever, Kukuruku disease from West Africa and Pacheco's parrot disease.

III. HEMOLYTIC

Pernicious anemia, hemolytic icterus, sickle-cell anemia, paroxysmal hemoglobinuria, mismatched transfusions, phenylhydrazine, sulfanilamide, cardiac decompensation (see above), septicemias, lobar pneumonia (*q.v.*), malaria, icterus neonatorum, Hanot's cirrhosis, Lederer's anemia, following absorption of large hemorrhagic exudates.

The term "jaundice" is derived²⁴ from the old French *jaunisse*—*jaune* (yellow). It implies merely a staining of the tissues and fluids of the body with bilirubin. The commonest cause of icterus among young individuals (between the ages of fifteen and thirty) is acute catarrhal jaundice; this usually follows a benign, uneventful course. In older patients jaundice is commonly due to obstruction of the common bile duct by calculi¹⁰ or to pressure from carcinoma of the head of the pancreas.

Toxic or infectious jaundice results when damage to the liver parenchyma prevents bile pigments from passing through the liver cells to reach the biliary capillaries. This pigment then accumulates in the hepatic veins and enters the general circulation. Although hepatic degeneration is usually attended by no or only mild pain, this may be quite severe; likewise, obstruction of the common bile duct by stone is at times²¹ painless. Although most instances of jaundice in elderly patients are obstructive, acute liver injury may occur at any age. Gallstones have been found in children three years of age; these have rarely caused jaundice. Gallstones will produce jaundice only if they are obstructing the common bile duct; stones remaining in the gallbladder will not be associated with jaundice.

Diagnosis of the Jaundiced Patient.—In the diagnosis of the jaundiced patient, a complete history and thorough physical examination are of prime importance. In about three fourths of the cases, diagnosis can be made at the bedside on

the basis of the history.²⁶ Frequently, additional information can be supplied by complete blood count; urinalysis including examination for bilirubin, urobilin, and bile salts; blood Wassermann reaction; careful biliary drainages; stool examinations; blood chemistry (van den Bergh, icterus index, blood urea nitrogen, cholesterol and cholesterol esters, serum protein, serum phosphatase), liver function tests (galactose, hippuric acid, glucose tolerance, etc.), Takata-Ara test, roentgen examination of the gastro-intestinal tract, blood fragility test, examination for sickle cells, etc. Roentgen examination of the gallbladder should not be performed routinely in patients with obstructive jaundice. Cholecystogram has not proved of value in demonstrating the gallbladder in patients with obstructive jaundice²⁹; when such an obstruction is near the duodenum, this procedure may result in pancreatitis. Further damage to the liver may also occur under such circumstances. It has been possible, however, to demonstrate the gallbladder roentgenographically in 7 or 8 cases of catarrhal jaundice.³⁷ A bromsulfalein test is of no value in differentiating obstructive from other forms of jaundice inasmuch as the bromsulfalein is reabsorbed into the blood stream after excretion by the liver if biliary obstruction is present.

Frequency of Causes of Jaundice.—It is of some assistance to recognize the comparative frequency of the various causes of jaundice. This depends largely upon whether the physician is a surgeon or an internist; the latter sees a large number of patients with acute catarrhal jaundice which are only rarely admitted to a hospital. In private practice, it has been my experience that 90 per cent of jaundiced patients under the age of thirty have acute catarrhal jaundice, and that this disease is by far more common than any other form of jaundice. In a large series of clinic cases,³⁹ 30 per cent of the jaundice was caused by carcinoma (of the head of the pancreas, gallbladder, bile ducts and metastatic); in 25 per cent, the icterus resulted from obstruction of the bile ducts by gallstones or associated conditions; in another 25 per cent, a toxic or infectious cause was found; in 7 per cent, the jaundice was hemolytic in nature; in another 7 per cent a benign stricture was at fault; other causes were rather rare. Snell³⁹ has stated that excluding hemolytic jaundice and stricture (which are

usually readily diagnosed), there are 2 chances in 3 that the jaundice is obstructive in nature, and 1 chance in 2 that a neoplasm will be found; these figures apply to individuals above thirty years of age. My personal experience has shown that obstructive gallstones are much more common than neoplastic obstruction of the common bile duct.

Acute Catarrhal Jaundice.—The commonest form of all jaundice is acute catarrhal jaundice. The clinical picture of this condition is relatively constant. It is usually sporadic in occurrence but occasionally is found in several members of a family. The disease has also been observed in epidemic form, lending further support to the belief that it is infectious in origin. The typical picture is as follows: a youth, aged eighteen, feels rather tired and achy, and consults a physician because of general malaise. He has had no important symptoms. Physical examination is essentially negative at this time except for a slight fever of from 99° to 102° F. Following a day or two in bed, the temperature returns to normal, but the patient begins to complain of epigastric distress and soreness. Slight or marked nausea, and occasionally vomiting may occur. A definite icteric tint can now be detected in the sclera and palate; the patient will also have noticed that his urine has become dark and his stools light in color. Pruritus may or may not occur. The liver is slightly enlarged and tender and the spleen is not infrequently palpable. Blood count usually reveals a moderate leukopenia with a relative lymphocytosis. Bilirubin and urobilin are usually present in the urine. During the next several days, the stools become progressively lighter in color, while the urine and skin become darker. About one week after the onset of visible jaundice, the skin color will usually have reached its height, and will begin to fade. This gradual lessening of the jaundice may consume a period of from one to five weeks. For a very short interval, at the height of the jaundice, bile pigment may be completely absent from the stool; this persists for only a day or two at most, and usually a small amount of bile pigment will be detected in the stool by chemical examination.

A galactose liver function test done at the height of the jaundice will usually show a decreased tolerance. Galactose is converted (with difficulty) into glycogen by the normal liver.

Normally, or in mild obstructive jaundice, if the patient is given 40 Gm. of galactose in a pint of water (after a twelve-hour fast), 3 Gm. or less of galactose are excreted in the urine within five hours. The kidney has no threshold for galactose so that if this is not converted into glycogen by the liver, as long as it remains in the circulation it will be excreted in the urine. In jaundice resulting from liver damage, the excretion amounts to 4 or 5 Gm. or more during the first five hours. The galactose liver function test is no longer considered as a method of differentiating conclusively between obstructive and toxic (primarily hepatic) jaundice; in over 25 per cent of patients with advanced obstructive jaundice (as in gallstones, pancreatic carcinoma, strictures of the common duct, etc.) there will appear a decreased galactose tolerance because of the associated hepatic damage.

The treatment of acute catarrhal jaundice is conservative; rest in bed is advised during the period of fever and gastrointestinal irritability. This is usually not more than three or four days. The preferred diet is one high in carbohydrate, low in fat, and containing about 14 per cent of protein. Fruit juices are especially well tolerated by these patients. Livers containing sufficient glycogen and a low fat content are usually less susceptible to the action of toxic agents. Because of the absence or decrease of bile in the intestinal tract during the acute stage of the disease, fats are not well digested and are often not tolerated. In view of the present concept that acute catarrhal jaundice is a mild form of hepatic degeneration,²⁶ it is not believed that stimulation of biliary secretion by decholin is of importance in its treatment; however, many clinicians continue to employ (with success) small daily doses (4 Gm.) of magnesium sulfate (which relaxes the sphincter of Oddi) or biliary drainages until the jaundice has disappeared.

The etiology of acute catarrhal jaundice is unknown; it is considered to be an infectious disease. Certain observers feel that it is the result of an acute gastroduodenal catarrh resulting in obstruction of the biliary passages by obstruction of the mouth of the common bile duct from the swollen mucous membrane of the duodenum, by an ascending cholangitis,¹⁸ by a plug of mucus obstructing the mouth of the common bile duct or by spasm of the sphincter of Oddi following an inflammatory

duodenitis. It is their belief that the liver is affected only in rare cases when the jaundice persists for a considerable period of time. Most clinicians believe, however, that acute catarrhal jaundice is a form of mild toxic degeneration of the liver.

In England, infectious jaundice is divided into 2 groups: (1) Weil's disease and (2) epidemic catarrhal jaundice or infective hepatitis. The common sporadic form of acute catarrhal jaundice is considered to be a separate disease due to an ascending cholangitis following dietary indiscretions or an upper respiratory tract infection.⁴ Infective hepatic jaundice or infective hepatitis is thought to be a toxic form of acute hepatitis.³

Occasionally some patients, in whom the condition seems to be a mild catarrhal jaundice, develop a chronic hepatitis. Unfortunately the etiology of chronic hepatitis with jaundice is obscure and these diseases are not well understood. Graham has pointed out the relationship between long-standing gallstone disease and hepatitis. All forms of hepatitis usually exhibit a slight and fairly constant jaundice; the biliary passages are not obstructed. There is commonly a firm, smooth enlargement of the liver and spleen with very little evidence of hepatic damage. Many of these patients live for years⁴⁰ in fairly good health.

Toxic Hepatitis.—The liver may be greatly enlarged from toxic changes and sections often show a yellow appearance from excessive deposition of fat in the liver cells, as in delayed chloroform poisoning, in fatal acidosis in children and in phosphorus poisoning when death occurs early.⁴² The term cirrhosis was originally applied to the yellow appearance of these livers; recently this has been restricted to the occurrence of fibrosis in this organ. Chloroform, carbon tetrachloride, and arsphenamine usually produce central necrosis²⁸ while the virus of yellow fever characteristically involves the midzonal portions of the lobule; the periportal region is commonly affected in eclampsia. There are no characteristic findings or symptoms for injury of the central or of the peripheral portions of the lobules alone.³⁴

Arsphenamine jaundice often occurs during the course of antisyphilitic treatment but does not necessarily depend upon

the amount of drug given or the stage of the disease. The incidence of jaundice in untreated syphilis averages 0.18 per cent⁴⁵; jaundice occurs in arsphenamine treated cases in approximately 0.85 per cent of the patients.^{38, 41} In a series of 18,000 patients who received antisyphilitic treatment at a large institution over the course of fifteen years, 158 persons developed jaundice. It was found that arsphenamine caused jaundice one and one half times as often as neoarsphenamine. In this series,⁴¹ postarsphenamine jaundice was almost three times as common in the white as in the colored patients. No relationship was found between the stage of the disease during which the patient received treatment and the frequency of jaundice. Approximately two thirds of the cases of postarsphenamine jaundice occurred during or after the completion of the first 10 injections of arsphenamine. There was no correlation between the amount of drug used and the development of jaundice. Jaundice was also reported in several patients following the injection of bismuth subsalicylate.

The symptoms and physical findings of postarsphenamine jaundice are quite similar to those of acute catarrhal jaundice⁴⁵ so that a differential diagnosis can usually be made only by the history. The course of the reaction is usually mild. Although right upper quadrant pain may occur in a minority of these individuals, it is not severe enough to be confused with acute gallbladder disease. There is usually a slight fever persisting for approximately five days. Symptoms usually disappear within one or two weeks after the onset of the jaundice. The liver is somewhat enlarged and the tip of the spleen can occasionally be felt. Acute yellow atrophy (acute necrosis) of the liver occurs in about 5 per cent of the patients with arsphenamine hepatitis.

The liver, with its enormous blood supply, is invaded by spirochetes during their early dissemination¹⁹ in syphilis; however, extensive acute hepatitis is uncommon in the early stages of syphilis.

Toxic jaundice following the administration of *cinchophen* is extremely uncommon; however, the mortality in cinchophen hepatitis is approximately 50 per cent. It has been estimated³⁹ that not more than 1 person will be affected among 250,000 taking this drug. A susceptible individual may die following

the ingestion of only a few grains of cinchophen. Phenylcinchoninic acid (cinchophen) was discovered in 1887 and was first used medically (as atophan) in 1908. Almost 100 anti-rheumatic remedies have been found³⁰ on the market which contain the toxic quinoline radical; unfortunately many of these are sold under trade names so that neither the physician nor the patient may be aware of their contents.

Cinchophen and its derivatives (neocinchophen, etc.) have been widely used in the treatment of gout and arthritis. Almost 50 tons are consumed yearly in this country. Two hundred cases of jaundice following cinchophen have been reported²⁷ with a mortality of 46 per cent. In contradistinction to this, one large arthritic clinic has used cinchophen (with caution) in the treatment of 2500 cases of arthritis over a ten-year period without a single incidence of liver damage.

Deaths have also followed the administration of neocinchophen. Trade names for this drug include tolysin and novatophan. In spite of the rarity of the jaundice following cinchophen, the high mortality attending such a complication and the lack of therapy therefore argue against the use of drugs containing this compound. After a careful study of this problem,²⁷ no safe method was found for administration of this drug.

Intravenous administration of lead in the treatment of inoperable carcinoma has been followed by toxic jaundice. Acute liver cell degeneration has also been produced by the eating of poisonous fungi (mistaken for edible mushrooms). Food poisoning is occasionally accompanied by jaundice. This also occurs frequently in acute streptococcal infections, severe tonsillitis or acute sinusitis, and may accompany staphylococcal infections, typhoid or paratyphoid fever (appearing about the end of the second week), and influenza (especially the so-called "intestinal" type). Jaundice is not common in typhoid fever even though there are usually numerous foci of necrosis scattered throughout the liver.³⁵

Jaundice following ingestion of phenobarbital is almost unknown, having been reported in only 2 patients.^{7, 28} In the recorded cases, jaundice appeared in a male, aet. fifty, following a dose of 1 grain of phenobarbital daily for twenty-two days;

in the second case, jaundice followed in fourteen days after the daily consumption of $1\frac{1}{2}$ grains of the drug.

Weil's Disease.—One of the uncommon causes of infectious jaundice in this country is Weil's disease, also known as spirochetal jaundice or spirochaetosis icterohemorrhagica. Many instances of this disease have been reported in Europe, Japan, and the East Indies. Not more than 10 proved cases have been described in the United States; in a recent outbreak of jaundice in Detroit, the Weil organisms could not be isolated in more than 1 case. The virulent Weil strain has not been found except in places accessible to wild rats.²⁰ The organisms are carried in the renal tubules of the rat and are excreted in the urine. The spirochete has been found in approximately 10 per cent of rats all over the world. For all practical purposes, the rat is the main source of infection for man.

Active immunization may be produced against Weil's disease by vaccination. Clinically, after an incubation period of approximately one week, the patient with this disease develops a severe chill, high fever, headache, herpes (often becoming hemorrhagic), muscular pains and prostration. In the second stage of the disease which occurs about five days later, hepatic and generalized lymph node enlargement, and jaundice (in half of the cases), are noted. Hemorrhagic manifestations appear in most of the patients. The third stage, occurring about one week later, is marked by gradual improvement in the patient's condition.

Because of the usefulness of serum if given early, diagnosis must be made as soon as possible. Among the available diagnostic aids are²⁰ darkfield examination of a thick smear of blood plasma after the erythrocytes have been precipitated by centrifuging at low speed; darkfield examination of the urinary sediment (after ten days) from 50 cc. of freshly voided urine; guinea-pig inoculation; blood culture (special technic); agglutination reactions (positive after the first week of the disease); complement fixation (with an antigen made from a culture of the spirochetes); and a precipitation test. In the differential diagnosis one must consider infectious jaundice from other causes, acute catarrhal jaundice, acute yellow atrophy and yellow fever.

The occurrence of jaundice in patients with *toxic goiter*

has been commented upon not infrequently.^{2, 44} By means of the galactose liver function test, impairment in liver function has been demonstrated in patients with hyperthyroidism. The injection of the serum of thyrotoxic patients into white mice has produced in these animals livers free from glycogen and more susceptible to damage.²⁵ The feeding of desiccated thyroid gland to the cat, rat, mouse, guinea-pig or rabbit produces a reduction in liver glycogen.¹¹ Jaundice was found to occur in not more than 20 per cent of 107 fatal cases of exophthalmic goiter coming to autopsy; the liver lesions in these patients included⁵ acute fatty degeneration with central necrosis, simple atrophy and toxic cirrhosis. These were intimately related to the severity of the disease.

Severe jaundice is not a common complication of *pneumonia*. In a series of 860 cases of lobar and bronchopneumonia over a three-year period,⁶ only 2 had severe jaundice due to the pneumonia. A slight icteric tinge is rather frequent and latent jaundice as manifest by the van den Bergh reaction is an almost constant occurrence⁹ in pneumonia. In various acute infectious diseases, including pneumonia, cloudy swelling of the liver cells is an early change; changes in the cells due to anoxemia and actual necrosis of the liver cells may occur.

Jaundice frequently accompanies *congestive heart failure*. This is a result of several factors including anoxemia and increased blood destruction, liver damage resulting therefrom, etc. Severe liver injury is produced by anoxia. Marked jaundice is uncommon following a coronary artery occlusion; however, this has been reported¹⁶ appearing four days after the occurrence of a coronary occlusion and disappearing nine days later.

The term acute yellow atrophy is actually a misnomer inasmuch as the pathologic change in this condition is a necrosis rather than an atrophy; the liver is at times larger than normal (in the acute cases), and its color may be reddish rather than yellow in prolonged cases.⁴⁶ Acute necrosis of the liver is usually the result of some toxic cause. Its symptoms include nausea, vomiting, gastric irritation, a dry, furred tongue, headache, and later, delirium, drowsiness, stupor, coma and convulsions. The outcome is usually fatal within several days after the onset of the acute necrosis.

Jaundice developing early in the *puerperium* is rather rare. In a series of 39,000 births, catarrhal jaundice was noted¹⁵ in the *puerperium* on only 3 occasions, all of the patients being primiparae.

Yellow fever is very uncommon in this country. Cirrhosis practically never occurs in those who recover from the disease because the virus is neutralized by immune bodies as early as the fourth day of the fever.¹²

Jaundice has also accompanied *gonorrheal infections* in patients where a gonorrheal perihepatitis has followed a pelvic inflammatory disease and also in gonorrheal septicemias with endocarditis.⁴² A toxic hepatitis has also occasionally followed pyelitis and instrumentation of the lower urinary tract (*Dour-mashkin's syndrome*).

Differential Diagnosis.—There is no absolute method of differentiation between biliary obstruction and primary liver cell damage. A detailed history, including a careful inquiry as to the use of drugs, the location and type of pain, the rapidity of onset of the icterus and a family incidence of jaundice will often prove valuable. A sudden colicky pain with rapidly developing jaundice usually indicates stone or infectious obstruction of the bile ducts. A dull heavy stretching continuous pain is often associated with hepatic degeneration and malignancy.¹⁷

On physical examination, special points to be noted include the intensity and color of the jaundice (yellow, green, reddish), the size of the liver and spleen, irregularities in the surface of the liver, the presence of a palpably enlarged gallbladder, abdominal masses (gastric or pelvic malignancy), Ewald node, periumbilical ring of metastases, ascites and the general nutrition of the patient. If a specimen of stool is not available for inspection, it is practically always possible to obtain a few particles by inserting the gloved finger into the rectum. In the time allotted, it will be impossible to discuss in detail the associated diagnostic aids in jaundice; however, a few pertinent points will be noted concerning the more important of these.

Cholesterol.—This is an alcohol which occurs in the blood serum in two forms, free, and combined as cholesterol esters (the latter form about 60 per cent of its total); it occurs

in the bile only in the free form. There is normally approximately 150 to 200 mg. per cent of cholesterol in the blood. Its site of formation and function are unknown. It may be increased in obstructive jaundice, hypothyroidism, diabetes mellitus, nephrosis, diseases of lipid metabolism (xanthomatosis, Hand-Schüller-Christian syndrome, Gaucher's disease, Niemann-Pick's syndrome, etc.), pregnancy, etc. It is usually decreased in starvation and inanition, severe liver parenchymal damage, hyperthyroidism and in late stages of obstructive jaundice (resulting in hepatic damage). It is similar to bile salts in its surface tension reducing property. It crystallizes out of solution with great ease and is retained in solution by the action of bile salts. With complete obstruction of the bile ducts, a value of 300 to 400 mg. per cent or more may be reached; this will remain high until late in the disease (when nutrition fails). Cholesterol is normally removed from the blood and excreted in the bile by the liver. In partial or intermittent obstruction (as with stone), it averages 250 to 300 mg. per cent.

The liver may form esters by combining cholesterol with fatty acids; these may be broken down by an esterase in the liver. In hepatic damage, cholesterol esters tend to decrease.^{43, 47} In obstructive jaundice, cholesterol esters increase but not in proportion to the increase in total cholesterol. Persistent absence of cholesterol esters from the blood in a jaundiced patient indicates severe liver damage and a poor prognosis.

Determination of the cholesterol fractions is a great aid in the differential diagnosis of jaundice; however, more than one determination should always be made. Absolute diagnostic reliance should not be placed on cholesterol results alone; this is merely an aid in diagnosis along with the history, physical examination and other procedures. The presence of liver cell damage, infection or cirrhosis will usually prevent the increase of cholesterol and cholesterol esters in obstructive jaundice.

Bilirubin, Urobilinogen, and Bile Salts.—Bilirubin, which is formed throughout the reticulo-endothelial system, is excreted by the liver. No important function has been ascribed to bilirubin except as an excretory product derived from the breakdown of hemoglobin.²³ Following the destruction of eryth-

rocytes throughout the body, the liberated hemoglobin is converted into hemosiderin and hematoidin; this latter compound does not contain iron, and is the precursor of bilirubin. The average normal serum bilirubin is from 0.1 to 0.5 mg. per 100 ml. Following its excretion into the small intestine, bilirubin is partially reduced to urobilinogen by bacterial action, and partially oxidized to biliverdin. A portion of the urobilinogen is absorbed into the blood stream and excreted again, mainly by the liver; a small amount is excreted by the kidneys. In the urine it is rapidly oxidized to urobilin. The exact function of urobilinogen is unknown. The major portion of the urobilinogen in the intestine is excreted in the feces as stercobilinogen (which is changed to stercobilin on exposure to sunlight).

Bile salts are formed only in the liver²² and are excreted into the intestine to aid in the digestion of fats; they are then reabsorbed into the portal circulation and reexcreted by the liver. Normally, bile salts do not appear in the urine.

Urobilinogen is formed by the action of intestinal bacteria on bilirubin. Its absence from the urine in a jaundiced patient denotes complete biliary obstruction. Excess of urobilinogen in the urine usually indicates patent bile ducts and liver damage, increased hemolysis, or both. None or only minute amounts of urobilinogen occur in normal urine. Increased urobilinogenuria is an early sign of hepatic damage as the ability to excrete urobilinogen is one of the first functions to fail in a diseased liver. Urobilinogenuria does not definitely rule out obstructive jaundice as, in cases of long-standing jaundice, bilirubin may be excreted into the colon; in addition, it is possible for urobilinogen to be formed in the bile ducts in the presence of infection.

Toxic or infectious jaundice is accompanied by an absence of bilirubin from the urine unless an obstructive element is present (in which case bilirubin appears in the urine when the renal threshold is exceeded), the presence of urobilinogen in the urine and stercobilinogen in the stool. No bile salts will appear in the urine as extensive liver damage decreases their formation. Obstructive jaundice shows bilirubinuria but no urobilinogen in the urine or stool (if the obstruction is complete); this is subject to the conditions mentioned in the

preceding paragraph. Bile salts accumulate in the blood stream and appear in the urine.

The presence of bile salts in the urine indicates obstructive jaundice without much liver damage; disappearance of bile salts from the urine in obstructive jaundice is a sign of marked liver damage (as bile salts are manufactured by liver cells). In catarrhal jaundice bile salts are rarely present in the urine because of the associated liver damage.

Icterus Index and van den Bergh.—The van den Bergh reaction is of value in differentiating hemolytic from obstructive and toxic jaundice. The intensity of the jaundice can usually be followed rather accurately by the van den Bergh reaction. Articles of food, such as carrots, egg yolk, orange juice, etc., may color the blood serum and produce a marked elevation of the icterus index; this must always be borne in mind when this test is employed.

In obstructive forms of jaundice, there is an immediate direct van den Bergh reaction, a greatly increased indirect reading, and a very high icterus index; in toxic or infectious jaundice, the direct van den Bergh is delayed or biphasic, the indirect reaction is greatly increased and the icterus index is high. In hemolytic forms of jaundice the direct van den Bergh reaction will be negative or delayed and the indirect reading and icterus index will be slightly or moderately elevated. Not more than 10 per cent of functioning liver tissue is necessary for ordinary requirements of pigment excretion so that marked liver damage may occur before this is reflected in the van den Bergh test or icterus index. The rationale of the van den Bergh reaction is well presented by Machella.²²

Serum Protein.—Serum proteins are decreased in proportion to the extent of the parenchymatous liver damage; however, decrease occurs only if extensive liver damage is present. They are decreased only late in obstructive jaundice unless there has been preceding liver damage. A tendency toward inversion of the albumin globulin ratio accompanies this decrease.

Serum Phosphatase.—Phosphatase is normally present in both blood serum and bile. It was formerly considered by some³⁹ that the serum phosphatase was increased in biliary obstruction and was normal or decreased in hepatogenous

jaundice. Experimental obstruction of the common bile duct in dogs produces a marked rise¹ in the serum phosphatase; this is also elevated but to a lesser degree in experimentally produced toxic jaundice. Recent clinical experience⁸ has shown that because of wide overlapping of values in the 2 groups, the determination of serum phosphatase is of no value in differentiating toxic from obstructive forms of jaundice.

Galactose Tolerance Test.—This has been commented upon earlier. It is extremely important to remember that many of the most important hepatic functions can be maintained when only 20 per cent or less of the liver is normal.³⁴ Sugar tolerance tests are not of great clinical value in determining liver damage; such tests may be normal in the presence of marked liver destruction.

A marked decrease in tolerance, usually occurs in severe parenchymal liver damage. There is no decrease in tolerance in obstructive jaundice until late in the disease. The results of this test are roughly comparable to those of the hippuric acid tests.^{32, 39} The hippuric acid conjugation test of Quick may be of some value in patients with doubtful liver injury.

Tyrosinuria.—The presence of tyrosine in the urine in small amounts suggests liver damage or new growth; large amounts of tyrosine are found in the urine in acute liver parenchymal damage.

Diagnostic Pointers.—Opinions vary as to the value of the presence of *pruritus* as a factor in differential diagnosis. Some individuals have found this to be most severe in obstructive jaundice³⁶ from calculus and malignancy, while others feel that *pruritus* does not materially aid in differentiating obstructive from primary hepatic jaundice.³⁶ *Pruritus* is probably due to the presence of large amounts of bile salts in the blood stream. In the author's experience, *pruritus* has not been present unless obstructive jaundice has occurred. When marked liver damage has occurred following biliary obstruction, bile salts decrease in the blood stream and the itching disappears.

The color of the jaundice has been commented upon; jaundice of primary hepatic injury is often orange yellow, while in obstructive jaundice this is usually greenish. In biliary obstruction due to carcinoma, the bilirubinemia

(after reaching its peak) is characterized by its relative constancy. In approximately 50 per cent of those cases of biliary obstruction due to carcinoma of the head of the pancreas, a distended gallbladder can be felt; this is sometimes confused with a Riedl lobe of the liver. Both complete obstruction of the common bile duct and acute degeneration of the liver may produce extremely high figures in the icterus index (300 or more). The intensity of the jaundice is not a good criterion of the clinical symptoms or prognosis. Persistent absence of bile from the stools for more than a week is almost always indicative of obstruction of the common bile duct by a malignant tumor. In obstruction due to stone, bile can usually be obtained by repeated biliary drainages. Excess fat in the stools of a jaundiced patient may completely mask the color of bile pigment.

Treatment of Infectious and Toxic Jaundice.—This consists in immediate removal of the toxic substance if possible and the use of a diet high in carbohydrate, low in fat, and containing approximately 14 per cent of protein; 14 per cent of protein in the diet has been found by Channon to displace liver fat as well as choline. It is possible to produce³³ a high liver glycogen in dogs with common duct obstruction by large intravenous injections of glucose and a high intake of carbohydrate orally. A greatly increased glycogen level does not protect the liver against injury if there is a high level of fat present³³; the protective rôle of carbohydrate probably depends upon its displacement of the liver fat during the deposition of liver glycogen.¹⁴

If a high carbohydrate diet cannot be employed (300–500 Gm. daily), large amounts of glucose are given intravenously. An experimental toxic state can be produced in dogs with damaged livers by ingestion of meat²⁶; it has been suggested, therefore, that the proteins be in the form of milk, cheese and egg white. Since the liver uses glycine as a detoxicating agent,²⁶ 5 to 10 Gm. of gelatin may be added to the daily diet. Animals fed on diets rich in fats are extremely susceptible to the toxic action of chloroform¹² while a high carbohydrate diet protects against such poisoning. In dogs poisoned with arspenamine, however, the reverse is true.

Marked liver damage results in an increase in the pro-

thrombin time and in hemorrhagic phenomena. Ravdin and his co-workers³³ have shown that the use of large amounts of carbohydrate by mouth and by vein as well as blood transfusions preoperatively and postoperatively did not reduce the incidence of postoperative hemorrhage but did markedly diminish the degree and extent of the hemorrhage and the mortality.

Vitamin K may prove of benefit in the treatment of the hemorrhagic diathesis of obstructive jaundice. It has been shown that vitamin K is a food accessory factor required for the synthesis of prothrombin. In chicks deprived of vitamin K, a 50 per cent decrease in the prothrombin concentration was found as early as the fourth day.³¹ Hemorrhages readily occurred when the prothrombin fell under 20 per cent. A definite decrease of prothrombin occurs in biliary obstruction; this is probably a cause of the bleeding in jaundice.

Vitamin K is contained in large amounts in powdered alfalfa and is normally present in abundance in the intestinal tract. It is a fat-soluble vitamin; in patients with obstructive jaundice, one should supply not only vitamin K but bile salts in addition, to aid in the absorption of the vitamin K. A good source of vitamin K is a mixture of 85 per cent oat plants and 15 per cent wheat plants (8 inches high), cut close to the ground and dried within two and one-half minutes of the time of cutting; these must be pulverized and refrigerated. In cases of obstructive jaundice with hemorrhagic phenomena, we are now using 1 drachm of this substance (in orange juice or in capsules) and bile salts (Bilron, Lilly, 10 grains) by mouth three times daily.

In operations upon jaundiced patients, spinal anesthesia should be used³³; chloroform, avertin, divinyl ether and prolonged diethyl ether may cause liver injury; gas mixtures are contraindicated because of the marked sensitivity of liver cells to reduced oxygen tension.¹³

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THE NEWER CONCEPTION OF THE TREATMENT OF SCIATICA AND NEURITIS

As we contemplate the treatment of sciatica and neuritis it is of great encouragement to note the steady improvement and simplification which therapeutic measures have undergone in the past. It is equally inspiring to consider the various and interesting methods, both medical and surgical, being currently introduced for the further relief of these affections.

It is common knowledge that prolonged pain in the distribution of the two main components of the sciatic nerve, the external and internal popliteal nerves, may result from a variety of causes. Authorities agree that there are comparatively few cases recorded in literature of true sciatic neuralgia and that most cases of this nature can usually be classified as secondary sciatica. The affection may exist for months or years and the patient may experience remissions but, at the end of such periods, no evidence will be manifested of organic disease except, perhaps, a degree of change in the Achilles reflex and some muscular wasting. Because of its persistency and consequent effect on the morale of the patient, the intractable pain should be arrested whenever possible. Very often the diagnosis of sciatica has the same vague clinical significance as the term rheumatism. At times, any painful condition radiating in the posterior aspect of the thigh, regardless of its etiology, is often erroneously labeled sciatica. As pain constitutes the chief criterion, the quality and intensity is the main concern of the patient. In the early stages it may be trifling and then progress to pain of great intensity. In the study of a case, one must determine whether he is concerned with a sciatic neuralgia or a case of true sciatic neuritis. Pain may

be remittent or intermittent and intensified by trivial factors, *i. e.*, exposure to draughts, motion of affected limb or by neighborhood pressure. There may be associated muscle spasm and mild sensory disturbances such as hyperesthesia or paresthesia along the lumbosacral distribution. There is no alteration or change in the power of the affected limb and the tendo achillis reflex is physiologic. In the literature, x-ray findings in such a case show no pathology and they may be regarded as essential sciatica or sciatic neuralgia. This condition is to be differentiated from true sciatica or neuritis which constitutes inflammatory involvement of the nerve.

Sciatic neuritis may be of the primary type resulting from generalized toxemia, alcohol, lead, arsenic, diabetes or syphilis. Secondary types begin as unilateral phenomena and later present the typical sciatic syndrome when it is caused by pressure on the lumbosacral nerve roots before it leaves the pelvis and are due to such lesions as spinal cord tumor or compression by rupture of the nucleus pulposus, *i. e.*, intervertebral disk injury, malignant involvement of the spine or osteo-arthritis of the spine. The treatment of these groups will not be discussed in this paper.

The reflex neuralgias embrace the more frequent types and are usually preceded by symptoms of muscle insufficiency in the back and sacro-iliac regions. There is an intermittent ache and tiredness associated with stiffness and soreness and accompanied by muscle spasm. A protective tilt may be present. Generalized nervous fatigue and irritability, due to physical strain, weak feet and varicosities are frequently encountered. The chief symptom is pain in the lumbosacral region or hip joint and it tends to spread downward. It may be sudden or gradual in onset, often severe, especially at night, and is worse in the sitting posture. The definite characteristics are indicated by the fact that the patient lies on his side with flexion of the hip and knee joints and plantar flexion of the ankle. There are special points of tenderness (*a*) between the ischial tuberosity and great trochanter, (*b*) center of posterior aspect of thigh, (*c*) lateral to the middle of the popliteal space, (*d*) middle of calf, (*e*) behind the medial malleolus. Abnormalities of the vertebrae such as occult spinal bifida, anomalies of the transverse process of the fifth lumbar vertebra and sac-

ralization or impingement of the same vertebra, afford areas of special vulnerability and may predispose to injury under strain. Postural defects are predisposing factors where the muscles are chronically overworked. Such conditions as abnormal curves of low spine, increase of the anterior load, imbalance of pelvis or lateral imbalance, scoliosis, spondylolisthesis, *i. e.*, slipping of the fourth or fifth lumbar vertebra, or both, forward on the sacrum. Disease of the sacro-iliac joints, whether tuberculous or nontuberculous, osteomyelitis, malignancy, osteo-arthritis or injury to the spine may cause imbalance or osteo-arthritic changes and produce a sciatica secondarily. It is, therefore, quite apparent that the basic treatment should eradicate the underlying cause whether it is due to foci of infection, resulting toxic states, rheumatic or orthopedic factors. In conditions where the sciatic disturbance is secondary, as in a metastatic, neoplastic or tuberculous process in the spine or pelvis, it should be designated as a sciatic syndrome in contradistinction to true sciatica.

Treatment.—Treatment may be divided as follows: (1) Palliative, (2) neurosurgical, (3) orthopedic. In the management of a patient complaining of pain in the distribution of the sciatic nerve the most important factor is to make an accurate diagnosis. There are so many pathological conditions giving rise to pain in the distribution of the sciatic nerve that without a correct diagnosis intelligent treatment cannot be administered. It is obvious that such conditions as sacro-iliac arthritis, luxation, spondylitis deformans, disease of the hip joint and cord neoplasm are strictly surgical or orthopedic procedures. Routine removal of all focal infection is indicated. Some go so far as to claim that there is no idiopathic sciatica and obviously there should always be a cause. Regardless of the truth of this statement, there are many cases in which relief can be accomplished by methods of treatment which are symptomatic and carry no necessity of proving a definite etiological factor. Even when a distinct surgical or orthopedic condition is the cause of pain in the sciatic nerve, treatment directed to the symptoms will relieve pain while appropriate treatment is directed to the cause. The surgical or orthopedic treatment will vary with the cause and must be left to those skilled in this work.

Palliative Treatment.—The first and most important consideration for symptomatic relief of pain is rest. Any motion producing pain in an inflamed nerve is harmful and increases the disability. Some cases are so acute that it is impossible to move the part due to pain. Obviously, any case in which pain is aggravated by motion should be put at complete rest until the acute stage subsides. Splinting may have to be employed to secure absolute rest and, in some instances, the use of Buck's extension is the best solution to the problem. The fact that the part must be kept at rest is not a contraindication to the use of other remedies. The simplest and most useful analgesic we can use is heat in its various forms. The hot-water bag or the electric heating pad may be applied in the most acute cases. This relieves pain quickly and efficiently and causes an increased blood supply to the part which is one of the factors in overcoming the inflammation and restoring the nerve to normal. These applications can be applied continuously in mild degree and are most beneficial in all stages. As soon as the patient is able to move the part, it is best to resort to the infra-red lamp because its rays are more penetrating and consequently more effective. Such applications can be given from one-half to one hour and repeated several times a day. For the more penetrating types of heat we must employ the high frequency current. Conventional diathermy, which has a wavelength of 300 meters, has been utilized for many years in the treatment of sciatic pain. This current must be applied by means of metal electrodes in contact with the skin. Because of the variations in resistance of the various tissues of the body, the heating is unequal and must last from twenty to sixty minutes in order that the blood supply can produce an equalized heating throughout the part. Our experience has been that this is the best form of high frequency current to use when we have a large mass of tissue to heat, such as an entire leg. Treatment must last one-half hour or more. If the pain is purely referred and considered as neuralgia, without any signs of sciatic neuritis, it is better to apply the electrodes front and back covering the sacro-iliac joints and the sacrosciatic notch and treat through and through.

The next most efficient method of applying deep heat is the use of short wave diathermy, employing the coil technic.

The induced current sets up eddy currents in the tissue which results in the formation of deep heat. This has been found the best method of producing deep heat with the short wave current. Another form of treatment is the use of static electricity. The static wave current is both diagnostic and curative. The prime conductors are separated so that a spark passes through them and each time a spark passes a massive contraction of all the tissue under the electrode takes place. The treatment lasts for twenty minutes and the length of the spark is gradually increased according to the patient's tolerance. If there is any spasm of the surrounding muscles, this is followed by static spark which is very effective in affording relief.

An important application in the treatment of sciatic pain is the use of the rapid sinusoidal current as advocated by Ulanski.¹ This is a sinusoidal current of 110 voltage with 7200 interruptions per minute. One electrode is placed on the sacrosciatic notch and the other on the posterior aspect of the knee or ankle. The current is started and then increased to the point where a tonic spasm occurs in the muscles and is maintained for one minute and then gradually reduced. Just how this current acts is not understood but the result is usually a prompt and lasting relief from pain. It is not claimed that the treatment is curative, but it does relieve pain and thus gives you a chance to continue with your treatment of the lesion in the nerve. After a number of years of using this technic, we feel that it is a dependable and efficient aid in the treatment of sciatic pain as it not only relieves the pain but, by encouraging the patient, enables you to carry out treatment which will eventually remove the pathology.

When these ordinary physiotherapeutic measures have afforded no relief, x-ray exposures have proved effectual in 60 per cent in a series of 72 cases which we have studied. The area treated covered the lumbosacral region and the distribution of the nerve. Deep therapy is employed. One half mm. of copper and 1 mm. of aluminum filtration, 200 kilovolt, is used. Small doses are just as effective as larger ones and only between 100 and 200 roentgen units are required. The skin target distance being 50 cm., caution must be observed to keep this form of treatment within safe limits so as

not to damage the skin. This procedure is followed every fifth or seventh day and the clinical response, in favorable cases, should be apparent after the fourth treatment.

Neurosurgical Treatment.—The injection into the sciatic nerve itself of different solutions such as saline, alcohol, quinine and urea hydrochloride have been tried and the results, in many cases, have been favorable. Pain may be controlled by the injection of alcohol into the area about the sciatic nerve or by the more direct injection into the subarachnoid space. It may cause a degree of degeneration of the sensory fibers but the motor fibers are usually unaffected. The success of this method depends upon the amount of alcohol injection and whether or not the alcohol is brought directly in contact with the nerve. The injection of 75 per cent alcohol usually paralyzes the sensory impulses with motor impairment. On the other hand, we must consider the fact that direct injection of alcohol into the nerve trunk destroys more of the nerve fibers than the perineural injection. In subarachnoid injections of alcohol, experimental evidence has shown that neuropathological changes incident to root involvement, motor and sensory alteration may occur. When this procedure is used, pain immediately subsides followed by numbness and a sense of warmth which includes the whole limb. This sequence of events substantiates the fact that pain fibers are conducted along with the thermic, tactile and pressure pathways. The injection of alcohol, however, has lost favor because of the danger of foot drop and paralysis of the muscles below the knee that might result. Due to the possibility of untoward effects, the alcohol technic, as a rule, should not be employed.

The injection of 2.5 per cent solution of formic acid has been recommended by Weeks,² the site of injection being previously anesthetized by 1 per cent solution of novocain. Four areas, the posterior and anterior surface of the thigh and two on the outer side of the leg, are marked with mercurochrome and in each area 3 or 4 minims of 1 per cent solution of novocain is injected fairly deep. After an interval of one or two minutes, 10 minims of formic acid solution is injected in each area with particular care being taken to insert the needle in the same puncture and in the same direction as the novocain injection. If there is no severe reaction, the

treatment is administered every second or third day until 6 or 8 injections are given, depending upon the response to treatment. The tissue at the site of the injection presents a hardened area which will ultimately disappear. A very satisfactory method of prompt relief may be obtained by epidural injections. The local anesthetic used is procaine hydrochloride, 2 per cent alkaline solution. The technic is as follows: A lumbar puncture needle is used with a glass syringe containing 20 cc. of the solution. The patient sits with his trunk bent well forward and his buttocks projecting slightly over the edge of the table. The projection formed by the elementary lamina of the fifth sacral vertebra is identified and between the 2 cornua the sacrococcygeal membrane is felt which feels elastic and yields to firm pressure. The needle is pushed perpendicularly through the membrane until it impinges on the anterior wall of the sacral canal, then the point of the needle is withdrawn slightly and its direction is changed until it runs upward for a distance of from 4 to 5 cm. The fluid is injected slowly—about five minutes is taken to empty the syringe. It is advisable to keep the patient in bed for three or four days thereafter. This technic is admittedly somewhat more difficult than injection in the sciatic nerve trunk which yields, as a rule, very satisfactory results.

Orthopedic Treatment.—Manipulative surgery has made tremendous progress in the relief of sciatic pain. It is one of the oldest forms of therapy but the methods are usually of delicate procedure and the technic must be exact, otherwise disastrous effects will be produced. Before employing manipulation, it is necessary to rule out osteomyelitis, acute infectious arthritis and neoplasm. The procedure is carried out by making a routine examination of the affected parts before attempting operative measures. The relief achieved is due, in part, to readjustment of the joints and principally to freeing adhesions or muscular spasms and the strengthening of shortening muscles.

In the past, the operation of choice was fusion resection of the transverse processes and subsequently fusions and bone grafts to the sacro-iliac joints have been extensively used. Most recent procedures, however, are sacral fusions with or without fusion of the sacro-iliac joints. Before attempting this

operative measure, one must be certain the joint to be fused is the underlying cause of the trouble and all other causative factors should be ruled out. Fusion is indicated when other more conservative measures have been unsuccessful and should be used only when there have been negative neurological findings, static types of pain and the patients are within the age limits of from twenty to fifty years. Reliable tests have not been established to determine with absolute certainty the involved joints. When doubt exists, it is best to fuse both joints and results indorse this procedure. Fusion may be carried out in a number of ways, the Smith-Petersen or Campbell technic being among the most favored. The postoperative period is still an important factor, four months being necessary for fairly good union of the graft and resumption of normal activity. Depending on the duration of the disability, complete union may take as long as a year. After union, rehabilitation and reestablishment of muscle strength may continue for months. Resection of facets, after lumbosacral fusion, has resulted in complete relief from pain and in some cases is essential for recovery. More accurate diagnostic methods are becoming of greater aid in the selection of cases for fusion operations and, in general, it has been found that patients whose pain is relieved by rest are most often benefited by fusion.

Freiberg³ has recently reported several important observations in the anatomic relations of the sciatic nerve. He states that the piriformis muscle is found to have its origin from the capsule of the sacro-iliac joint and therefore it is in close relationship with the sciatic nerve. Hence, this muscle may be expected to react by spasm as result of the disease in the sacro-iliac joint because of partial derivation from the capsule ligament of that joint. He obtained relief by cutting the iliotibial band when in contraction or by section of the piriformis muscle. This means, however, is only justifiable when relatively more simple and safe procedures have failed.

Neuritis may be classified etiologically. There are two varieties of peripheral neuritis; those caused by exogenous agents *per se* and those the result of dietary deficiencies. Schematically they may be outlined as follows:

I. Toxic:

(a) Inorganic salts and metals.

Notably lead, arsenicals and gold. Various others reported sporadically.

(b) Organic Compounds.

Apiol, triorthocresylphosphate and many others.

(c) Biologicals.

1. Vaccines—typhoid, staphylococcus, etc.

2. Bacteria—toxins. Diphtheria antitoxin.

II. Deficiencies:

(a) Organic diseases in the gastro-intestinal tract.

(b) Starvation and inanition.

(c) Imbalanced diet.

(d) Alcohol.

(e) Metabolic.

1. Vomiting of pregnancy.

2. Diabetes mellitus.

3. Pernicious anemia.

4. Wasting diseases.

Whether the etiology is directly due to toxic factors, infectious states or other innumerable causes, there is a corresponding inflammatory process in the peripheral nerve trunks which manifests itself clinically by pain on motion, weakness, sensory phenomena, atrophy of musculature and abolished tendon reflexes. Leukocytosis and pleocytosis may be present. The course may be gradual or rapid and intense and, if marked bulbar symptoms follow, fatal termination may result. However, the prognosis in the vast majority of cases can be considered favorable. Treatment depends upon the thorough investigation of the cause. Infectious or toxic neuritis may occur as a result of influenza, typhoid, lead, arsenic, carbon monoxide, Jamaica ginger extract or from possible foci in the tonsils, prostate or cervix. Pain resulting from rheumatic nodules in the muscles or myositis may be incorrectly labeled neuritis. The administration of serum therapy, particularly antistreptococcus and tetanus antitoxin, may be the etiological agent. The pathological changes in the nerve trunks are edema, resulting from an anaphylactic phenomenon similar to urticarial swelling. Selective action of the toxin may be shown by bilateral involvement of the brachial plexus and by optic neuritis. To avoid

these complications, sensitization and desensitization should be routinely employed before the administration of antitoxin.

Depilatory creams, containing thallium, may produce retrobulbar neuritis due to the affinity of the substance for the optic nerves. Because of low visual acuity and central scotomata, these cases are often regarded as intracranial tumor suspects but the bilateral sensory and motor involvement, especially of the lower limbs, and abdominal cramps, resembling lead colic, definitely indicates involvement of the lower motor neuron. The severe loss of vision in cases receiving sulfanilamide may be due to the toxic action of this drug. Additional symptoms may be headache, cyanosis, choking sensations and mild pain along the course of the peripheral nerve trunks. Due to the involvement of the hematopoietic system, it would be advisable to make frequent blood counts as a precautionary measure in all patients receiving this preparation. Upon the withdrawal of this drug the symptoms subside.

Since the introduction of hematoporphyrin (photodyn) it is becoming more and more widely used in promoting motor activity among cases of psychotic depression. Although its usage is purely empirical and it is considered harmless, the literature now contains references to neuritic complications following the administration of photodyn. Recently, Thorner⁴ reported a case of polyneuritis occurring after 4 injections, at weekly intervals, with recovery following the discontinuance of this drug.

Acute infectious polyneuritis is an unusually rare condition which may be caused by organisms or a filtrable virus. It usually affects the males from ten to thirty years of age. It may occur in three distinct forms: first, there is a polyneuritis involving all extremities associated with moderate febrile reactions 101° to 103° F. and various eye palsies which progresses rapidly; second, there is a variety which shows similar peripheral involvement of all extremities but is accompanied by cranial nerve impairment, particularly the seventh nerve, associated with various bulbar phenomena; third, there is a group which begins by involvement of the legs, spreads rapidly to the muscles of respiration and the upper extremities and closely resembles the Landry type of paralysis. In these forms, the paralyzed muscles are of the flaccid type, exhibiting

moderate amount of atrophy, and the deep tendon reflexes are usually hypoactive or entirely abolished. The paralysis may be either proximal or distal. The prognosis is favorable except where the bulbar phenomena become intense. The index to recovery may be based on the cerebrospinal fluid studies. While the manometric readings may be slightly above normal, clear fluid with slight protein reaction constitutes, as a rule, favorable prognosis. A yellowish spinal fluid with high protein, usually, indicates a less favorable prognosis. The following is a report which comes under this classification:

E. T., aged fifteen, school boy, was admitted to the Jefferson Hospital on May 25, 1938, with complete flaccid paralysis of all extremities and with bulbar phenomena; he was intensely toxic and dehydrated with marked cyanosis. His history reveals he was a full-term baby, normal delivery; had measles and chickenpox before the age of six; was vaccinated for smallpox but was never Schick tested. With the exception of sore throats, he had been well since school age. Three weeks before, while in bed one night, he cried out and told his mother he felt hot. The next morning he remained in bed complaining of a sore throat and feeling ill. He was given laxatives and gargles with temporary improvement in about three days. Two weeks later, he complained of pains over the right lumbar spine and numbness in the ulnar portions of both hands. He was taken to a doctor who studied him thoroughly and found albumin in the urine and hypertension 150/80. He placed the patient on treatment and suitable diet. Then it was noticed that the right side of his face became swollen and the right corner of his mouth drooped. The same day, it was found that when he walked he slapped both feet and complained of weakness to the extent of not being able to walk. The numbness in his arms persisted and gradually involved the entire extremities. At this time his urine was albumin free. He then developed such severe pains in his legs that when touched he would scream. Flaccid paralysis of both legs followed with gradual ascending weakness and loss of power of the upper limbs. His condition became progressively worse. He vomited almost everything. Nausea and vomiting, accompanied by abdominal pains, persisted for two weeks, but the paresthesia disappeared. A day later he developed vomiting of bilious material and choked on attempt to swallow. On the morning of May 25, he developed three convulsive states, which occurred in rapid sequence and lasted two hours. Since the onset of the disease he has had tachycardia (100-150).

On admission the patient was poorly nourished and showed evidence of marked reduction in weight. He was semistuporous and could be aroused with difficulty. He appeared toxic, cyanotic and dehydrated. There was no nuchal rigidity. The right pupil was larger than the left, both were dilated. Their reaction to light was sluggish, more pronounced on the right. Pressure over the supra-orbital nerves failed to elicit evidence of a facial paralysis. There appeared to be a very slight ptosis on the right. The fundi were negative. Eye muscle movements could not be definitely determined at this time but

several days later were found to be normal. There was bilateral weakness of the soft palate. The tongue was protruded in the midline. The thyroid was not palpable. There was a flaccid paralysis of the extremities and beginning muscular atrophy with absent deep tendon reflexes and tenderness along all superficial nerve trunks. There was beginning bilateral foot drop, more pronounced on the left. Kernig and Babinski signs were absent. Slight movement or pressure of the limbs produced intense pain. There was priapism and incontinence of retention. A blowing mitral systolic murmur was heard over the precordium. On admission his temperature was 103° F.; pulse 112, respirations 22.

During his first week's stay at the hospital, his temperature fluctuated from 100° to 105.6° F. In the course of several weeks his temperature became normal. Laboratory findings were as follows: Hemoglobin, 55 per cent; red blood corpuscles, 3,180,000; white blood corpuscles, 36,000. Blood and spinal fluid Wassermann were negative. Spinal fluid pressure was 125 mm. H₂O. Queckenstedt was negative. The fluid was clear, colorless, with normal sugar and a slight increase of protein; 1 cell per cubic millimeter. Nose and throat cultures showed predominance of *Streptococcus haemolyticus*. There were normal electrical reactions of the musculature. Urine was negative except for plus 2 albumin; nonprotein nitrogen and blood sugar were within normal limits.

Progress. For three weeks prior to admission the child received very little liquid nourishment because of inability to swallow. Catheterization was required for several days due to retention. A tremendous amount of salivation persisted for about five days; vomiting of a slight amount of mucus for several days. For a week, there was a moderate amount of delirium and confusion. There were no voluntary movements of the extremities for ten days, then gradual return of motion in the upper limbs was noted and four days later, despite the marked degree of wasting, the power of the lower extremities was partially restored. His sensorium became clear at the end of the second week at the hospital. Our impression was that we were dealing with an acute infectious polyneuritis associated with bulbar phenomena and vesical disturbance. The epileptiform convulsive attacks were of toxic origin, probably due to cerebral circulatory interference, with the production of cerebral anoxemia.

Treatment. On admission he was placed in an oxygen tent for twenty-four hours. Fifty cc. of 10 per cent glucose by venoclysis was given daily for four days. Gastrostomy feedings every three hours, by Murphy drip, was given for two weeks following which he was able to swallow large amounts of solid food. Sodium phenobarbital, 1½ grains, intramuscularly, every three hours, for 8 doses, controlled the epileptiform attacks. Twenty grains of sulfanilamide were given every fourth hour for three days and then 10 grains three times a day for four days. Five drops of tincture stramonium, three times a day, in the course of ten days, controlled his salivation. He received 10 mg. of vitamin B intravenously three times a day during his stay at the hospital. His acute symptoms subsided on the eighteenth day. Light massage together with galvanism were then instituted. His foot drop was treated by placing the parts in physiologic position by means of adhesive strips.

He was discharged at the end of three weeks with partial return of motor power and in a fairly comfortable condition. He was placed on ½ cc. reticu-

logon every three days because of his anemia and vitamin deficiency and was also given strychnine sulfate, $\frac{1}{40}$ grain, three times a day.

This case is of interest because we were dealing with a boy who had hypertensive cardiovascular disease. Because of a history that a member of his family had diphtheria four weeks earlier and the patient's early symptom of sore throat, he was regarded, for a time, as a case of postdiphtheritic polyneuritis. The absence of *Bacillus diphtheriae* and the predominance of *Streptococcus haemolyticus* in the throat culture changes the etiological concept. The association of a convulsive state and vesical disturbance was an unusual complication.

Our evaluation of the concept of a deficiency neuritis is still in the process of metamorphosis and there are many who believe that most of the neuritides still classified etiologically as due to exotoxins are, in reality, the result of a deficiency. Although descriptions of polyneuritis are to be found in the literature of antiquity, it was not until the early part of the seventeenth century that lead colic with a peripheral paralysis was described.⁵ A century and a half later, John Coakly Lettson,⁶ in 1787, first described "alcoholic" polyneuritis and James Jackson⁷ presented the same picture independently in 1821. In 1848, Robert J. Graves⁷ suggested that the lesions were to be found in the peripheral nerves and Louis Dumenil⁷ demonstrated them in 1864. Largely through the work of the latter's successors, Lancereaux, Gombault and Joffroy,⁷ peripheral neuritis was accepted as a clinical entity in 1880.

Early investigators were of the opinion that the lesions were caused by a neurotoxin such as alcohol, lead or the "toxins" of pregnancy. As early as 1897, Christian Eijkman,⁸ studying beriberi in the Dutch East Indies, suspected that a dietary deficiency was a cause of the polyneuritis. In 1914, Cooper⁹ demonstrated the therapeutic efficacy of yeast in avitamin polyneuritis but no one thought of applying these observations to the common human varieties until 1928. That year Shattuck¹⁰ suggested the relationship and the similarity was again pointed out by Minot¹¹ in 1929. However, it was Wechsler,¹² in 1930, who attempted a clinical study. Following his preliminary paper, Wechsler,¹³ in 1933, brought forth evidence of the common etiologic factor in the majority of

peripheral neuritides. He presented 9 cases of peripheral paralysis of divergent etiology, all improved or cured by high caloric, high vitamin dietary regimen. He classified them as follows: 2 cases of uncomplicated chronic alcoholism, 1 of atypical pernicious anemia with alcoholism, 1 of postcholecystectomy vomiting, 2 voluntary dietary restrictions of which 1 was bordering on beriberi, 1 case of carcinoma of the stomach, 1 associated with tuberculosis and 1 with pernicious nausea and vomiting of pregnancy. He also points out that the histopathology in beriberi and other peripheral neuritides is identical and, therefore, the etiologic agent must be the same. There is a demonstrable deficiency in all of the cases. All of them were relieved by a high vitamin B diet. Wechsler has recently proposed a revision in nomenclature based on his clinical experience. He classifies two distinct groups, one in which there is definite evidence of inflammation of the peripheral nerve trunks which forms a comparatively small group of cases and another group in which there is distinct degeneration of the nerve trunks; the latter pathologic change occurs in the greater majority of cases which he terms as multiple peripheral neuropathy. This concept is more precise and deserves general acceptance because the pathologic change in the nerve fiber, following the effects of alcohol, lead, carbon monoxide, diabetes, etc., is not an inflammatory reaction but the end-results are those of degenerative processes.

Continuing an amazing volume of clinical investigation in this country, Cowgill¹⁴ and his workers showed that the B₁ needs of an organism were dependent upon the caloric intake and the metabolic state and that the requirements were proportionate to both. He formulated the vitamin-caloric ration and by means of it was able to determine the minimum requirements and the actual deficit. Following these studies, Strauss¹⁵ added to the picture by exposing the rôle of the gastro-intestinal tract, namely, its malfunction in precipitating the polyneuritis. He discussed his own work with the intrinsic gastric factor which facilitated the absorption of vitamin B₁ and was capable of improving the neuritis with an ordinary diet. He did not label the extrinsic factor unequivocally as B₁ although he admitted its relation to B₂. Later, however, Strauss¹⁶ gave 10 alcoholics, with severe polyneuritis, their cus-

tomary ration of alcohol—1 pint to 1 quart of whisky daily—enough theoretically to cause a paralysis and cured them of neurologic lesions by administering B₁ orally in massive doses.⁷ In 1936, Jolliffe¹⁷ and his associates, using Cowgill's ration, determined the vitamin B₁ deficiencies of a large series of alcoholics from whom reliable dietary histories were obtained and concluded and it took anywhere from seven to twenty-one days of absolute deficiency to produce a neuritis. By days of "absolute deficiency" is meant the calculable days in which no vitamin B₁ is ingested and is obtained by multiplying the period of deficiency by the estimated lack of vitamin B. These investigators proved that the length and severity of addiction had nothing to do with the production of neuritis. These studies were substantiated and expanded by Romano,¹⁸ Russell,¹⁹ Perkins,²⁰ Winans and Perry²¹ and A. H. Douthwaite.²² Perkins in particular pointed out the high incidence of achylia gastrica or hypochlorhydria. Thus we see that there are 2 factors in the production of a deficiency polyneuropathy; first, a gastro-intestinal tract which interferes with the proper absorption of the second or extrinsic element, vitamin B₁; and secondly, a dietary deficiency in the extrinsic factor. In the treatment of deficiency neuritis, it is hardly necessary to mention that the underlying cause should be eliminated where possible. In diabetes mellitus, neoplastic disease, and tuberculosis this is not immediately possible. It has been advised by many writers that the diet should contain around 4000 calories per diem. As will be shown shortly, the vitamin B₁ requirements on such a diet is amazing and the problem of administering it perplexing.

In our studies of 11 cases of alcoholic neuritis, 5 of whom were "solo" drinkers, there was marked evidence of food privation with resulting avitaminosis. The symptoms most frequently encountered were epigastric distress, anorexia, abdominal discomfort, diarrhea or constipation, fatigability, dyspnea on slight exertion, generalized paresthesia, tenderness, motor weakness and objective sensory changes. In all of these cases, the gastric contents showed absence of free hydrochloric acid and complete reduction in total acidity. Six cases had the blood picture of a macrocytic anemia. They received an injection of 1 cc. of reticulogen, a highly concentrated liver

extract plus B₁, every third day for 6 or 8 injections in conjunction with a balanced diet. The administration of this preparation shortens the acute stage, particularly in reference to the distressing pain and tenderness, and permits the earlier application of physical therapy. Improvement in general symptoms and the gastric and blood pictures occurred more rapidly. In some cases of alcoholic neuritis, changes may occur in the spinal cord, such as posterior lateral sclerosis or the development of Wernicke's encephalitis.

According to Cowgill's work on animals⁹ the maintenance ration for vitamin B₁ is 2.84 expressed units, or an absolute figure of 0.000284 when
$$\frac{\text{Vitamin B}_1 \text{ in grams}}{\text{Calories}} = R.$$

According to this formula, on a 4000-calorie diet, a normal individual requires $\frac{B_1}{4000} = R$ (0.000284). Although a high

figure B₁ = 11.36 crystalline B₁. The average individual ingests almost this much B₁ in a balanced diet of lesser caloric intake. However, experimentally Jolliffe and his co-workers have demonstrated that a ratio of 7 is necessary to cure the polyneuritis. Using Cowgill's formula, we find $\frac{B_1}{4000} = 0.007$;

B₁ = 28 Gm. crystalline vitamin B₁. During the acute phases of the neuritis, especially when there are gastric difficulties, crystalline vitamin B₁ can be administered daily, some intravenously in 10-Gm. doses and the remaining requirement given subcutaneously and orally. When the appetite returns and after the patient's vitamin requirements are reduced, the intravenous route may be discontinued. According to Jolliffe, in addition to the massive intravenous doses there should be a high intake of vitamins A and C.

Romano¹⁸ outlines his diet as follows: 4000 to 5000 calories (high protein—low carbohydrates); dried brewers' yeast—4 Gm.; wheat germ—30 to 60 grains; B₁ or liver parenterally (intravenously and intramuscularly); fresh fruit juices, cod liver oil or haliver oil.

The chronic alcoholic, whose ingestion of calories in the form of alcohol indirectly decreases the total intake of B₁ by his limitation of food produces an avitaminosis. Inasmuch

as there is associated gastro-intestinal disturbances there is an added interference with the effective absorption of the limited amount of B_1 that is required in the diet. It has been definitely shown that the B_1 requirement is directly proportional to body weight, caloric intake and metabolism. Infections or toxic conditions may raise the total metabolism and not infrequently precipitate the acute symptom.

The neural manifestations in such a deficiency consists of gradual impairment of sensation advancing proximally from the distal portion of the extremities. The motor disturbances are characterized by paresis of the feet progressing upward and extending to the upper limbs. However, this sequence may be reversed, the weakness beginning in the hands and arms and progressing downward. An individual addicted to alcohol, who in addition has poor tolerance for the liquor, now presents a fertile field for the further development and progression of sensory loss and flaccid paralysis. While the primary symptoms may be attributed to the qualitative and quantitative deficiency of B_1 , the end-results are produced by alcoholic excesses. When the polyneuritis is acute and not too extensive, one may observe remission of symptoms and signs in the course of several weeks. When nerve degeneration has existed over a long period of time, and has progressed to an advanced stage, a correspondingly longer period must ensue before restoration of function occurs.

SUMMARY

Sciatica.

1. Uncover the underlying and basic factors of the sciatica and their removal when possible.
2. Careful neurological and orthopedic examination and appropriate x-ray studies to exclude the presence of sciatic syndrome resulting from the primary conditions, such as, infectious arthritis, metastatic processes, cord tumor or herniation of a ruptured intervertebral disk.
3. Routine palliative measures should be the initial treatment. Short wave diathermy, x-ray exposures and rapid sinusoidal current usually yield the most effective results in the mild form of treatment.
4. In resistant cases, when mild measures have been inef-

extract plus B_1 , every third day for 6 or 8 injections in conjunction with a balanced diet. The administration of this preparation shortens the acute stage, particularly in reference to the distressing pain and tenderness, and permits the earlier application of physical therapy. Improvement in general symptoms and the gastric and blood pictures occurred more rapidly. In some cases of alcoholic neuritis, changes may occur in the spinal cord, such as posterior lateral sclerosis or the development of Wernicke's encephalitis.

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3. Routine palliative measures should be the initial treatment. Short wave diathermy, x-ray exposures and rapid sinusoidal current usually yield the most effective results in the mild form of treatment.
4. In resistant cases, when mild measures have been inef-

fectual, the epidural injection of 2 per cent procaine hydrochloride is recommended.

5. Orthopedic measures such as fusion resection of the transverse processes or cutting of the iliotibial band and resection of the piriformis muscle should be attempted only when other means have failed. In long-standing cases, it may be necessary to operate and break up adhesions along the course of the sciatic nerve.

Neuritis.

1. Treatment depends upon the thorough investigation of its cause. When the etiology cannot be traced to the usual toxic infections or deficiency factors, seek unusual causes such as the administration of serum therapy, sulfanilamide, photodyn or the application of depilatory creams.

2. That changes in the peripheral nerve trunks are brought about by the lack of antineuritic component B₁ are quite uniformly accepted.

3. The administration of reticulogen, supplemented by a high caloric and well balanced diet, hastens the acute stage and promotes gastric and hemopoietic function thereby resulting in a more rapid clinical improvement.

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ALCOHOLIC POLYNEURITIS

UNTIL very recently clinicians, when confronted with a syndrome of multiple neuritis, were content to dismiss the diagnostic problem when the patient admitted imbibing from a pint to a quart of spiritous liquor a day, and considered the nerve affection the direct result of the toxic effects of alcohol. The medical profession in the past few years has been enlightened on the subject of polyneuritis with redirection of thought into different channels of physiopathogenesis. The specificity implied by alcoholic polyneuritis is now disregarded in favor of a more general conception since Shattuck, in 1928, first called attention to the occurrence of beriberi in persons with chronic alcoholism, cancer, diabetes, syphilis, marasmus of children, and pregnancy, all on the basis of an avitaminosis. Alcoholic polyneuritis, the toxic polyneuritis of pregnancy, diabetic, biliary and gastrogenous polyneuritides, postinfection polyneuritis, and the Korsakoff syndrome are clinically and pathologically identical with beriberi, differing only in the particular mechanism by which the deficiency is brought about.

That vitamin deficiency may be an etiologic factor in the development of polyneuritis in the alcohol addict has been substantiated by the work of Wechsler, Minot, Strauss and Cobb, Meyer, and others. The clinical and experimental work indicates that the alcohol addict with polyneuritis has, as a rule, a qualitatively inadequate intake of food and vitamins, and that the clinical manifestations and pathologic findings of beriberi and alcoholic polyneuritis are similar. These authors suggested, therefore, that vitamin B₁ deficiency may be the decisive factor in producing polyneuritis in alcohol addicts. It is interesting to note that the first case of polyneuritis and psychosis reported by Korsakoff in 1890 developed after preg-

nancy, and that similar cases have been described in puerperal infection, typhus fever, icterus and diabetes. It is well known, of course, that the syndrome occurs in chronic alcoholism, but so many cases have been reported following pregnancy that it is important to emphasize the observation that practically all instances of polyneuritis gravidarum were preceded by intractable vomiting and hence "starvation." Alcohol attacks the gastric mucosa and the liver resulting in loss of appetite and not infrequently vomiting. Many alcoholic individuals eat little and assimilate less because of impaired digestion. As a result of this they are starved and suffer avitaminosis. One is, therefore, dealing not only with a specific poison, alcohol, but with an additional factor, avitaminosis.

The chronic alcoholic addict usually ingests a sufficient amount of vitamin B for his caloric intake in the form of food, but each calorie received in the form of alcohol decreases the total intake of vitamin B and increases the requirements. Gastro-intestinal disturbances are not uncommon among steady drinkers and consequently the absorption of vitamin B may be reduced. The chronic alcoholic individual is thus prone to develop vitamin B deficiency. The avitaminosis is due not so much to the deficient ingestion of food as to the inability to digest, assimilate or metabolize because of the physical disorder which originally had nothing to do with the avitaminosis. Vitamin deficiency in turn causes lack of appetite which impairs further ingestion of vitamins thus setting up a vicious circle. Persons who consume large quantities of strong alcoholic beverages and fail to eat an adequate diet regularly are also particularly prone to develop pellagra. If, however, the chronic alcoholic addict continues to eat regularly of a diet adequate in the known essential food substances, he will usually not develop pellagra. Vitamins other than B have been shown to bring about degeneration of the nervous system. Mellanby showed that food rich in vitamins could prevent degeneration of the spinal cord by ergotoxin, and that the absence of vitamin A increases the degenerative effect of the toxin thus giving support to the suggested fact that it is not the endotoxin or exotoxin alone which brings about involvement of the nerves, but that the additional factor, avitaminosis, is the important one.

There is much clinical and experimental evidence to show that what passes for neuritis is not an inflammatory process, and that the pathologic changes demonstrated in most of the cases hitherto regarded as inflammatory are actually degenerative. It is true that there are cases in which there is inflammation of the peripheral nerves but these form a small group which is unrelated to the type of polyneuritis under consideration. There is every reason to expect a degenerative process in the cases of so-called "avitaminosis multiple neuritis," a pathological process such as is seen in the spinal cord and root lesions of pernicious anemia. This is exactly what occurs but the peripheral nerves are more involved selectively, although the spinal cord does not escape in many cases of peripheral neuropathy (Wechsler). Carmichael and Stern state that the "imbibition of alcohol lowers resistance and permits degeneration of the nervous system through the action of toxins or through lack of essential nutritive factors." They point to the occurrence of simple chromatolysis and parenchymatous changes, to the absence of neuronophagia and to the essential degenerative process in the peripheral nerves as well as occasional degeneration of the posterior columns. In view of the fact that lipochrome deposits are found in chronic alcoholism and pellagra, they suggest food deficiency as a common factor which permits the toxins to act on the nerve cells.

Recent fundamental contributions have made possible a more direct approach to the study of the etiology of syndromes suspected of being on the basis of vitamin B deficiency. The first of these contributions was Cowgill's determination of the vitamin B requirement of man and of a formula by which this requirement can be predicted. He has shown that the vitamin B requirement of man is directly proportional to body weight, caloric intake and metabolism. He recognized that the vitamin requirement with relation to the diet is estimated not only in the ratio of vitamin intake to body weight, but also with reference to the total caloric intake of the individual. He expresses the true vitamin value in a fraction:

$$\frac{\text{vitamin B mg. equivalent}}{\text{calories}}$$

The importance of the calories derived from alcohol in relation to vitamin B requirement can be illustrated by using Cowgill's calculation of the vit./cal. ratio of Sherman's average American diet. This diet contains 6847 mg. equivalents of vitamin B and 2500 calories, and gives a vit./cal. ratio of 2.74. This ratio, by reference to Cowgill's prediction chart, is adequate for a 96-Kg. man. An individual who supplements this diet with 1 pint of whisky daily adds about 1600 calories to the denominator of the equation. The vit./cal. ratio now becomes 1.67, which is only adequate for a 60-Kg. man. The 96-Kg. man or any individual weighing more than 60 Kg. on this vitamin B and caloric consumption would theoretically show evidence in time of vitamin B deficiency. Clinically, the opinion that vitamin B₁ deficiency plays a large rôle in alcoholic polyneuritis was based primarily on the following observations: First, that patients with alcoholic polyneuritis had, as a rule, an inadequate food intake; second, that alcoholic polyneuritis and beriberi showed similar clinical and pathologic manifestations. In addition it was observed that these subjects improved when such diets were supplemented by vitamin B₁ concentrates and that improvement occurred even while the subjects were given from a pint to a quart of whisky daily. The next fundamental contribution was the production of crystalline vitamin B₁ in amounts sufficient for clinical investigation.

Minot, Strauss and Cobb made a study of 57 patients with undoubted alcoholic polyneuritis. Forty-one had eaten little fresh food of any kind for at least a number of months, and in some instances for several years. Fractional gastric analyses were performed on 43 patients; only 7 had a normal secretion of free hydrochloric acid, 21 secreted no hydrochloric acid and 15 had diminished amounts. Fourteen of the 57 patients had dermatitis and edema which could be related to a deficiency of protein. Forty of the 57 patients were treated by a diet rich in protein, minerals and vitamins, and it was observed that recovery took place more uniformly and with greater rapidity than previously. It was concluded that dietary deficiency, especially the lack of vitamin B₁ plays an important rôle in the production of alcoholic polyneuritis. Fifty per cent of their cases showed evidence of pernicious anemia, pellagra and

sprue, conditions in which gastric anacidity is encountered in the majority of instances. In 1935, M. B. Strauss selected 10 patients with uncomplicated alcoholic polyneuritis for study, and by careful questioning the daily intake of spiritous liquor was determined in each case. Such an amount (from 1 pint to 1 quart) of whisky was then administered daily to each patient throughout the period of study. At the same time each patient received, as a daily minimum of food, 2 eggs, 50 cc. of milk, 200 Gm. of beef or lamb, 240 cc. of orange juice, 4 servings of green vegetables, 90 Gm. of brewers' yeast or its equivalent, and by intramuscular injection a vitamin B₁ concentrate. Without exception the polyneuritis of each of these patients was relieved over a period of two to eighteen weeks during the constant administration of large quantities of whisky. He concluded that this condition does not result from a direct neurotoxic effect of alcohol, but is probably the result of a dietary deficiency, possibly conditioned in some cases by disturbed gastro-intestinal function and that it is similar to the polyneuritis of beriberi and should be treated accordingly.

In 1936 Perkins reported his studies of 82 cases of multiple neuritis of which many were associated with chronic alcoholism. These patients gave a history of long-continued use of alcohol, 30 of them with intestinal disturbances, loss of appetite, nausea, vomiting, gastric distress, diarrhea or constipation. In the majority of instances their diet had been inadequate both as to calories and balance. There were 15 cases of alcoholic pellagra; others showed mental disturbances as well as multiple neuritis. Five cases of Korsakoff's syndrome showed disturbance of attention, loss of orientation especially for time, defective memory especially for recent events, confabulation consisting of delusions and fantasied experiences; suggestion to suggestion and emotional instability were common manifestations. Ten patients showed multiple neuritis accompanying or following delirium tremens; 6 had no free hydrochloric acid, 4 showed diminished amounts of this secretion. All 10 had digestive disturbances and 8 had enlarged livers. These patients showed hyperesthesia of the skin and had the most pronounced tenderness along the nerve trunks of any of the patients in the alcoholic group. All of Perkins'

cases were treated by a diet rich in vitamins; brewers' yeast, orange and tomato juices, raw liver cocktails, liver extract, cod liver oil, peanut butter, quantities of milk, fresh vegetables, eggs and butter were included in the diet. The improvement seemed to be hastened in the cases of multiple neuritis with the exception of the Korsakoff syndrome. In these cases the neuritis disappeared and the patients gained in weight but the improvement in the mental state was very slow.

The evidence from the therapeutic tests confirms the view that patients with alcoholic polyneuritis suffer from avitaminosis, *i. e.*, they show recovery when foods rich in many vitamins are given. From the extensive clinical and experimental researches recorded in the literature the probability is that privation of vitamin B₁, or B₂ (G of the English), is the underlying cause of neuritis. However, it is possible that in every case in which there is a deficiency of antineuritic vitamins there must be an additional toxin or poison to bring about degenerative changes. It is quite possible that some of the supposed symptoms of vitamin B₁ deficiency in man are in part due to some other factor closely associated with vitamin B₁ in nature such as riboflavin (B₂), nicotinic acid and other compounds. Infection or excessive physical exertion, raising the total metabolism, not infrequently precipitates the acute symptoms of deficiency. Therefore, polyneuritis of beriberi or alcoholic types develops because complicating factors render the individual's vitamin B₁ intake inadequate.

The onset of vitamin B deficiency is generally insidious, but it may be sudden. The earliest manifestations are usually heaviness of the lower limbs and tenderness of the calf muscles with progressive motor disability in walking. At first the patient is aware of the motor disability in his legs after walking some distance and then he has the feeling as though his legs were going to collapse under him. A short rest overcomes this feeling and walking can be resumed. Various dysesthesias of the feet, such as burning of the soles and numbness of the toes, are early symptoms which gradually increase in intensity and spread upward. Shortly, weakness of dorsiflexion of the toes can be objectively demonstrated and there is diminution of the Achilles reflexes. Motor weakness gradually spreads upward to include the extensors of the foot, the calf muscles and,

finally, the extensors and flexors of the leg. Foot and toe drop is manifested by this time with loss of the Achilles and patellar reflexes while the sensory signs of hypesthesia advance up the leg and thigh in a stocking-like distribution. Degenerative changes in the muscles and skin are in evidence, the skin often becoming smooth and glossy. In many instances the neurological symptoms and signs are limited to the lower limbs but with further progression of the disorder similar symptoms and signs are complained of and noticed in the upper limbs. Occasionally, the hands and arms may be affected first and, as in the feet, the early symptoms are uncomfortable paresthesias and dysesthesias with weakness of the hands later evidenced by wrist drop. The tendon reflexes at the elbows are eventually lost and hypesthesia for vital sensations is followed by anesthesia in the periphery.

In severe cases confinement to bed is necessary because of the total disability of the patient who suffers great pain in the affected parts with cutaneous hyperesthesia, marked tenderness of the muscles and peripheral nerves to pressure, even the pressure of the bedclothes being intolerable. Control of the sphincters is generally not lost until the advanced stage or in debilitated persons. The cranial nerves are not usually involved except in such cases where there is associated with the multiple neuritis vascular lesions in the brain such as perivascular ring hemorrhages as are found in Wernicke's polioencephalitis hemorrhagica. Memory defects are commonly observed, and the patients with mental symptoms are generally cheerful and happy in spite of the severity of their disability and discomfort; however, marked mental depression is not infrequently observed. The Korsakoff syndrome is a well-recognized part of the clinical picture of alcoholic polyneuritis, the falsification of memory, confabulations and pseudoreminiscences being features of the symptom-complex.

Mouth lesions occur as complications of or as an essential part of the complex disease caused by the chronic use of alcohol. They occur very often and precede the serious condition known as alcoholic pellagra. Blankenhorn and Spies discuss this phase of the subject in their case study of 73 patients recognized as alcoholic pellagrins, and 125 cases of pellagra, 95 per cent of which were known to be chronic alcoholic

addicts. Eighty-eight per cent of the first group had mouth lesions and more than 50 per cent in the second group. They suggest that, because of the prevalence of these lesions, anyone addicted to alcohol who complains of weight loss, poor appetite or weakness be examined for oral lesions. Stomatitis and glossitis are the conditions referred to, the tongue, lips and buccal membranes, gums and palate are involved. The tongue becomes swollen and the teeth leave their impressions on the tongue at the sides and tip. The tongue has an exaggerated redness and becomes a beefy red color, ulcers occasionally appearing along the sides and tip. These authors have found that the lesions respond promptly to adequate vitamin therapy if it is started early in the course of the disease. The methods of treatment most efficacious in pellagra have likewise proved beneficial in treating the glossitis and stomatitis complicating chronic alcoholism (nicotinic acid particularly).

The polyneuritis of alcohol advances more or less rapidly in individual cases, and there is evidence to show that in the total absence of the antineuritic vitamin in the diet twenty days may be required for the appearance of the first symptoms; should no treatment be instituted the end-stages may be reached within a matter of weeks. Most patients suffer from a partial or irregular deficiency of vitamins; therefore, months may elapse before marked symptoms appear. Along the same lines, remissions and exacerbations are explained by temporary increase in the amounts of vitamins ingested and greater degrees of dietary inadequacy, respectively. Some cases of neuritis may remain in a relatively stationary condition for long periods because they partake of diets containing an amount of vitamin B which is insufficient for recovery but enough to prevent further progression. There probably are instances of unrecognized mild forms of the disease which are precipitated into severely acute attacks of multiple neuritis by infections or excessive physical activity. Cardiovascular complications are observed in severe cases of alcoholic polyneuritis such as dyspnea and palpitation on exertion, tachycardia and edema and occasionally sudden circulatory collapse. Rheumatic, arteriosclerotic or syphilitic heart disease may be present in addition to the damage due to vitamin deficiency.

The results of vitamin B therapy in the polyneuritic mani-

festations of beriberi, and equally applicable to the polyneuritis of chronic alcoholism, have been most satisfactory. When the polyneuritis is acute and not far advanced, one may observe complete remission of signs and symptoms in a matter of weeks. In subacute and chronic cases with evidence of progressive nerve degeneration over a long period a correspondingly greater time will be required for improvement and recovery to take place. Peripheral nerves are capable of regeneration as long as their ganglion cells in the anterior horns of the spinal cord and the posterior root ganglia are not damaged, because regeneration of completely degenerated cells and axis-cylinders within the central nervous system cannot take place. However, even under the latter conditions functional improvement not infrequently occurs with proper and adequate treatment. The therapeutic methods in use consist in the administration of a well-balanced, highly nutritious diet of at least 4000 calories a day supplemented by yeast or liver extract (B_1), and wheat germ (B_2). The present tendency in the use of vitamin B_1 in alcoholic polyneuritis is to give large doses, and since it has been shown that absorption from the intestinal tract may be so deficient as to preclude the administration of the vitamin by mouth, it is given parenterally in pure crystalline form. Treatment may be well initiated by the intravenous or intramuscular injection of 20 to 50 mg. of crystalline vitamin B_1 daily. This amount has appeared to be sufficient in all cases thus far observed and probably represents an excess over the actual requirement. After the two weeks of parenteral use, oral therapy may be substituted in the same dosage, or, where necessary, injections continued in a decreased dose of 10 mg. daily until the patient is relieved of all symptoms.

Brewers' yeast, plain or autolyzed, is a convenient means of administering not only vitamin B_1 but other portions of the B complex. Thirty Gm. of powdered brewers' yeast three times a day will generally be found beneficial in the less seriously ill patients, particularly if there is no gastro-intestinal distress which might interfere with the absorption of orally administered substances. It is probable that a diet deficient in vitamin B_1 may also be lacking in other portions of the vitamin B complex as well as vitamins A and C, and in iron and other minerals. This is suggested by the frequent occurrence of

glossitis, anemia and pellagra in association with beriberi. Therefore, it is advisable to provide, in addition to vitamin B₁, an adequate amount of vitamins A and C and iron, as well as foods rich in other portions of the vitamin B complex. Liver extracts in doses of 10 to 20 cc. intramuscularly every day has been especially efficacious in correcting glossitis and skin manifestations of the pellagrous type. Very recently, pure nicotine acid has been demonstrated to be a potent therapeutic agent for treating the mucous membrane lesions of pellagra. Spies, Cooper, Clark and Blankenhorn concluded that the average dose of nicotinic acid is 500 mg. daily, given in 5 doses of 100 mg. each, for the usual case of pellagra. One of the objects in vitamin B₁ therapy is to give an excess of the vitamin to provide for accumulation of vitamin reserve of this accessory food substance. Jolliffe has recently stated that the minimal therapeutic dose of vitamin B₁ which should be considered in the treatment of polyneuritis must be four times the daily minimal requirement of the vitamin. Cowgill places the daily requirement for vitamin B₁ at 10 international units per 100 calories of diet.

General nursing care and physiotherapy must not be neglected in favor of the newer therapeutic armamentarium in the treatment of multiple neuritis lest avoidable and irreparable complication develop. These patients are generally debilitated and are prone to develop decubitus ulcers and hypostatic pneumonia; therefore, scheduled change of position of the patient and careful hygiene of the back must be stressed. The principles of physiotherapy are to be supplied to cases of polyneuritis with no particular alteration, the aim being to improve muscle tone, stimulate peripheral circulation and prevent contracture through faulty posture.

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CLINIC OF DR. MICHAEL G. WOHL

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AN EVALUATION OF ENDOCRINE PREPARATIONS, THEIR USE AND DOSAGE

ENDOCRINOLOGY has made amazing strides in the past decade in laboratory and experimental knowledge; applied organotherapy in the clinic, however, has failed to keep pace with it. Certain factors present themselves which limit the applicability of hormone therapy, and it is apropos at this point to review briefly what they are.

I. Depression of Function of Substituted Gland.—It is a well known fact that a ductless gland is not stimulated by its own secretion; therefore, endocrine replacement therapy has to be used continuously for a long time. It is unfortunate that frequently when certain gland extracts are continually injected, there is a tendency for the substituted gland to undergo atrophy and depression of function.¹ Obviously such a course of events tends to defeat our purpose in the long run. Not all glands display this tendency, as it has been shown that the islands of Langerhans in diabetes mellitus improve in function on insulin therapy.

II. Production of Antihormones and Suppression of Secretion of Other Glands.—The prolonged use of glandular products may produce a refractory state because of antihormone formation (Collip). Antagonistic effects may be evoked by inhibiting the secretion of other glands; attempts have been made to use this factor to advantage, as the use of theelin in suppressing the diabetogenic function of the pituitary gland.¹² For the present, at least, this procedure in the clinic seems unwarranted until further proof is forthcoming.



Relations to Autonomic Nervous System.—Certain endocrine disorders are prone to manifest themselves by an intense disturbance of the autonomic nervous system. In Graves' disease, for example, the common manifestations reflect sympathetic stimulation; this results in increased pulse rate, rise in blood pressure, dilation of the pupils and increased sweating. Occasionally stimulation of the parasympathetics dominates the picture and the chief symptoms may be bradycardia and gastro-intestinal manifestations. Such an instance was recently reported by one of us.⁴ The menopause is likewise characterized by bizarre upsets of the autonomic system, more of which will be said in an ensuing section. In the treatment of disorders of these types, recourse must be had to various measures, including psychotherapy, sedation and the use of drugs not necessarily of glandular nature (calcium, phenobarbital, ergotamine, atropine, etc.).

Relation to Vitamins.—Interrelationships between vitamins and hormones have often been commented upon in recent literature, particularly since the structural formulae of both groups are rapidly being brought to light. The similarity of vitamins D₂ and E and the sex hormones to each other and the cholesterol group is very striking. The effects of vitamins and hormones are sometimes parallel. Greene⁵ has called attention to the similarity of gastro-intestinal, psychic, neurologic, and to a certain degree the dermatological manifestations of pellagra and myxedema. An instance of multiple deficiency simulating polyglandular syndrome came to our attention recently. Vitamin administration brought about greater improvement in her case than glandular therapy (Fig. 178). Apparently hormonal function is conditioned greatly by adequate vitamin intake. Thus it has been conclusively demonstrated that animals deficient in vitamin B are lacking in gonadotropic hormone of the anterior pituitary.⁶ On the other hand, it has been shown that vitamins may inhibit the physiologic action of hormones. Thus there is clinical and laboratory evidence to indicate that vitamin A is a strong antagonist to thyroxin.^{6a}

CLINICAL ENDOCRINOPATHIES

Thyroid.—From a therapeutic point of view disturbances of the thyroid gland may be conveniently grouped into the

III. Variability of Tissue Response to Hormone Stimulation.—This can best be illustrated by the effect of desiccated thyroid on different tissues in different individuals. Equal amounts of this substance will produce different quantitative effects not only as far as cardiac, nervous, and other bodily tissues are concerned but also as regards the effect upon the basal rate.² The capacity of tissue to react varies also at different periods of life. Thus it is well known that in postmenopausal animals it is not possible to reactivate the ovary by any form of pituitary injection or implantation.³

IV. Inadequacy of Gland Products Totally to Replace Physiologic Secretions.—As a well-known example, we cite the use of desiccated thyroid in myxedema, in which condition thyroid medication is admittedly of inestimable value. Yet, we have been impressed by the frequency with which postoperative myxedema patients develop symptom-complexes of various types, even though they are treated with adequate maintenance doses of thyroid. Sometimes these symptoms relate to subacidity or achlorhydria, and require hydrochloric acid for their relief; at other times a hypochromic anemia develops, and responds to large doses of iron. Thus we see that desiccated thyroid cannot totally replace the effect of physiologic thyroid secretion especially in long-standing cases of myxedema.

V. Difficulty of Supplying Hormones According to Body Needs.—Sudden periodic influxes of glandular material into the body, such as would be represented by the injection method, is quite unlike the process of natural secretion. The oral route of administration would be more likely to duplicate the effects of nature, but unfortunately most gland substances are disintegrated by the gastro-intestinal juices. Thyroid and female follicular hormones are notable exceptions to this rule. The need of the body for hormones depends upon the physiologic demands placed on it; *e. g.*, excessive adrenalin secretion in hypoglycemia in order to liberate sugar from liver storage. The delicate regulatory mechanism of hormone supply according to demand is difficult to imitate by hormone therapy. We usually administer too much of the gland extract and are apt to provoke a countereffect.

tration (Lugol's solution in doses of 10 to 15 minims three times daily). The latter brings about a remission in seven to fourteen days. It is in this stage (involution) when the thyrotoxic process is to be interrupted by the surgical removal

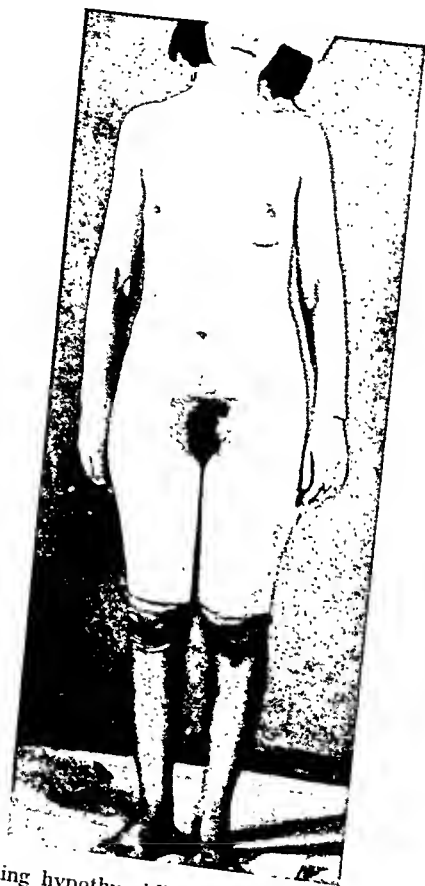


Fig. 179.—Illustrating hypothyroidism of the thin type in a woman aged thirty-six years. Tiredness; bizarre nervous manifestations; inability to gain weight. Pulse, 62. Blood pressure: systolic, 114; diastolic, 68. Basal metabolic rate, minus 19 per cent. Improvement under desiccated thyroid.

of almost all of the thyroid gland. The improvement is prompt and dramatic. Irradiation of the gland in selected cases is effective but is inferior to operation. It is to be stressed that iodine should be used only as a preoperative measure since it does not produce any permanent beneficial

hyperfunctioning and hypofunctioning types. Excessive action of the thyroid occurs as the toxic diffuse goiter (Graves' disease), toxic nodular goiter (toxic adenoma) and the atypical forms masked as heart disease, colitis⁷ and rarely as an acute

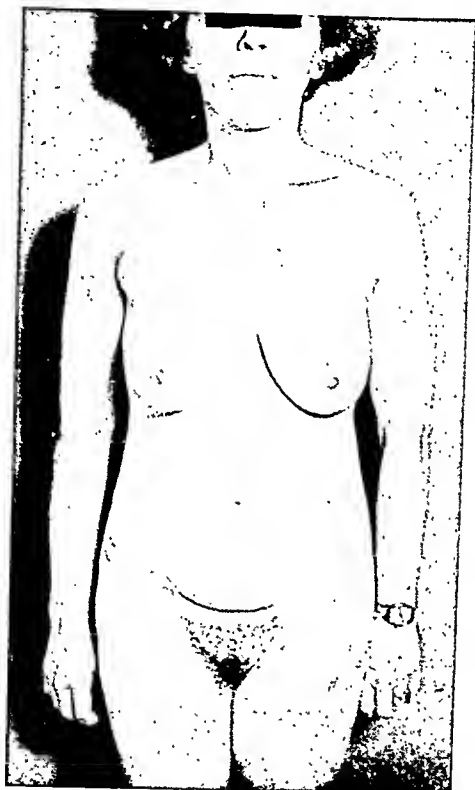


Fig. 178.—Multiple deficiency in a woman aged thirty-six years. Loss of weight, decreased menstruation, extreme weakness, anorexia, shooting pains in lower extremities, dizziness and swaying in the dark. Lived on restricted diet for two years (coffee, toast, broiled lamb and chicken). No vegetables, fruits or milk. Dry skin, brittle nails, carious teeth. Diminished reflexes and loss of hair. Basal metabolic rate minus 13 per cent. Gastric analysis showed free hydrochloric acid, minimum 20, maximum 60. x-Ray of sella turcica negative. Improved on high vitamin diet. Various endocrine preparations such as thyroid, insulin, antuitrin S, estrone, etc., failed to bring about improvement.

abdominal catastrophe.⁸ The plan of therapy consists in reducing the hyperactivity of the gland by complete mental and physical rest, proper diet especially rich in vitamin A and carbohydrates, sedatives (phenobarbital) and iodine adminis-

tration (Lugol's solution in doses of 10 to 15 minims three times daily). The latter brings about a remission in seven to fourteen days. It is in this stage (involution) when the thyrotoxic process is to be interrupted by the surgical removal



Fig. 179.—Illustrating hypothyroidism of the thin type in a woman aged thirty-six years. Tiredness; bizarre nervous manifestations; inability to gain weight. Pulse, 62. Blood pressure: systolic, 114; diastolic, 68. Basal metabolic rate, minus 19 per cent. Improvement under desiccated thyroid.

of almost all of the thyroid gland. The improvement is prompt and dramatic. Irradiation of the gland in selected cases is effective but is inferior to operation. It is to be stressed that iodine should be used only as a preoperative measure since it does not produce any permanent beneficial

effects on the course of the disease and may bring about an "iodine-fast stage." During this period the surgical risk is great.

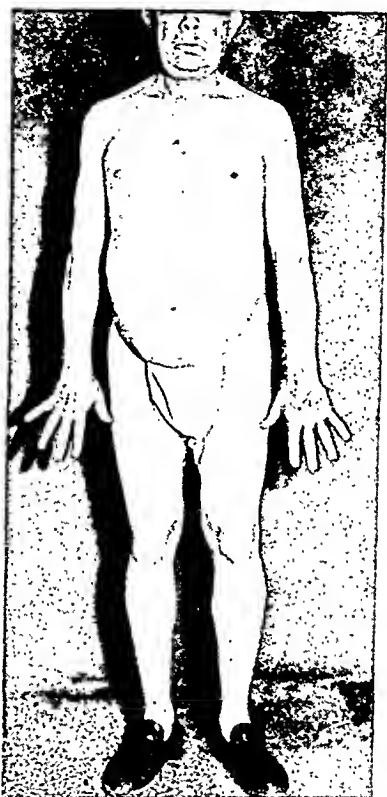


Fig. 180.—Illustrating myxedema masked as pernicious anemia in a man aged fifty-eight years. Weakness, loss of memory, unsteady gait, nervousness, constipation of two years' duration. Treated for two years with liver extract intramuscularly. Skin of body dry; brittle fingernails, lemon yellow tinge of face. Protruding abdomen (ascites). Pulse, 72. Blood pressure: systolic, 130; diastolic, 98. Basal metabolic rate, minus 32 per cent. Hemoglobin, 11 Gm. (65 per cent). Erythrocytes, 4 million per cubic millimeter of blood. Patient treated with desiccated thyroid, 3 grains daily, and reduced iron, 15 grains daily. After five months of treatment, he was greatly improved, ascites disappeared, basal metabolic rate, minus 2 per cent. At present, he is doing his usual work.

Hypothyroidism manifests itself in two main forms—cretinism in children and myxedema in adults. There are few diseases in which replacement therapy with desiccated thyroid

produces such miraculous changes as in myxedema. In cretinism the mental retardation and bodily underdevelopment are profound. In the first few weeks of treatment thyroid medication produces striking improvement but after a few months the results are disappointing, and when thyroid dosage is increased, toxic symptoms may ensue: loss of weight, insomnia, etc. Childhood myxedema, on the other hand, responds more favorably to thyroid extract. Full blown cases of spontaneous

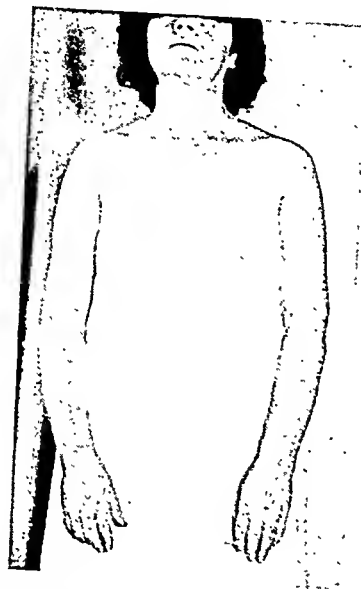


Fig. 181.—Spontaneous myxedema dominated by symptoms of psychosis. Mania, schizophrenic reactions. Basal metabolic rate, minus 35 per cent. Blood cholesterol, 400 mg. per cent. Prolonged use of desiccated thyroid (twelve months' treatment) brought about great improvement of myxedema with marked amelioration of psychosis.

adult myxedema are comparatively rare. Milder cases are quite common. They present themselves under various guises (Figs. 179–183). At times even the skilled clinician may require confirmatory evidence to prove his diagnosis. Three laboratory tests are available: the basal metabolic rate determination, blood cholesterol and radiological determination of bone age. In infants and children, the findings of a delay and late appearing centers of ossification is of great aid in establishing the diagnosis of hypothyroidism. Basal rate determinations

are unsatisfactory in children under six years of age. Blood cholesterol (normal values 175 to 200 mg. per 100 cc. blood) is definitely elevated in patients with hypothyroidism. The basal metabolic rate determination is the most widely used procedure in the diagnosis of thyroid disease. A decrease in the basal rate (less than minus 15 per cent) is generally



Fig. 182.—Myxedema heart. Generalized enlargement of heart; more to the left. Apex of heart in axilla. Patient's chief complaints were: shortness of breath on exertion, ankle edema, increase in weight and obstinate constipation. Pulse 68. Blood pressure: systolic 144, diastolic 102. Basal metabolic rate, minus 26 per cent. Blood cholesterol between 301 and 450 mg. per cent (on several occasions).

accepted as an indication of the existence of hypothyroidism. It is to be borne in mind that many states other than hypothyroidism may be associated with low basal rates and such patients may actually be harmed by thyroid medication. Addison's disease, and subclinical types of adrenal insufficiency are associated with low basal rates. In malnutrition, starvation,

constitutional asthenia, hypopituitarism and eunuchoidism one frequently finds low basal rates.

Treatment.—There are two different strengths of desiccated thyroid substances (exclusive of the crystalline hormone thyroxin). Thyroid U. S. P. (desiccated thyroid) is standardized to contain 0.17 to 0.23 per cent iodine. Another method of designating strength of thyroid preparations has grown out of the practice of some pharmaceutical houses to label their

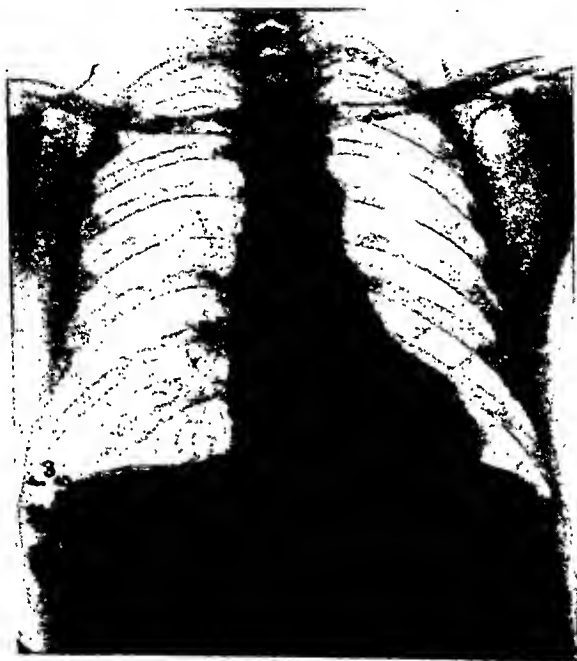


Fig. 183.—Same case as Fig. 182 after ten weeks of treatment with desiccated thyroid, the heart assumed normal size. (Courtesy of Dr. B. P. Widmann.)

product in terms of fresh rather than desiccated gland substance. One grain of desiccated thyroid gland substance is roughly equivalent to 5 grains of fresh gland. These variations in strength of preparations should be kept in mind when prescribing thyroid medication. It is safe to begin with $\frac{1}{2}$ grain of desiccated thyroid extract once or twice daily. If no untoward symptoms (nervousness, tachycardia, headache) develop within seven days, the dosage may be increased until a "maintenance dose" is reached. Most of the myxedema

patients are extremely sensitive to thyroid extract; hence the lower the basal rate the more gradually one should increase the thyroid extract. An initial large dose of thyroid extract may raise the basal metabolic rate abruptly in an individual who has been vegetating for a long time on a low plane of vitality and this sudden rise may produce unpleasant reactions. The

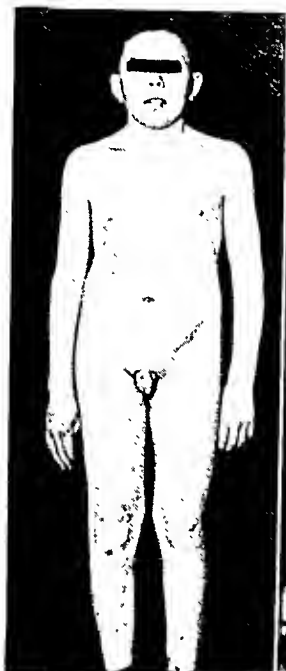


Fig. 184.



Fig. 185.

Fig. 184.—Aged eighteen years. Referred to clinic for growth hormone treatment because of underweight and stunted growth. Examination of eyes showed contraction of visual fields of right and left; pallor of disks. Calcified craniopharyngioma removed by Dr. Temple Fay.

Fig. 185.—Same case as Fig. 184. Sella turcica showed enlargement and deformity with encroachment on sphenoid sinus.

average maintenance dose is 3 grains daily. During the entire period of treatment the patient should be under a physician's supervision.

Thyroxin.—Pure crystalline thyroxin is now available for intravenous use. Dose 0.2 to 2 mg. In a myxedema patient, the physiological effect after a single injection does not appear until the eighth or tenth day. The rise in metabo-

lism may continue for three to four weeks. Some physicians administer thyroxin when desiccated thyroid has lost its effectiveness.^{8a}

Thyroid extract is also useful in some edemas (nephrosis) on account of its diuretic effect. In amenorrhea and Fröhlich's syndrome, it is prescribed for its stimulating effect on ovaries and pituitary gland. In some patients with obesity, desiccated thyroid is still a useful drug when given under a physician's supervision. It should be given in conjunction with a subcaloric diet. It is to be noted, however, that certain obese patients are very sensitive to thyroid extract in spite of their subnormal basal rate.⁹

Parathyroid Deficiency.—Parathormone or paroidin is a parathyroid extract used in postoperative tetany or spontaneous hypoparathyroidism. It raises blood calcium and lowers blood phosphorus. It is given intramuscularly (30 units); the dose is repeated twice or even four times daily. Its effect is enhanced by the simultaneous use of calcium salts, orally or parenterally. Recently a chemical substance known as "A.T. 10" (dihydrotachysterol) has been introduced in the treatment of tetany.¹⁰ In the acute cases, the average oral dose is 10 cc. daily for three days. In the chronic cases from 1 to 7 cc. weekly is claimed to be sufficient.

Pituitary Gland.—The pituitary gland is truly called the "master gland" of the body. Its multiplicity of functions is exercised by the posterior and anterior lobes. The posterior lobe yields a principle, pitressin, that is useful in surgical shock by its capacity to constrict capillaries thus raising blood pressure. Pitressin has also been used for the relief of intestinal atony in postoperative cases and to overcome the tympanitis of pneumonia. The latter function is due to its stimulating effect upon intestinal peristalsis. The andidiuretic effect of pitressin is made use of in controlling the polyuria of diabetes insipidus. It does not, however, cure the disease. The average dose is 0.5 to 1 cc. of pituitrin (containing pitressin fraction) given hypodermically from one to four times daily.

Pituitrin may also be used by nasal route either in the form of a tampon of absorbent cotton saturated with 0.5 to 1 cc. of the extract and inserted into one of the nostrils, or in the form of minute amounts of dried posterior pituitary powder

as a snuff. Another principle from the posterior lobe, pitocin, is used in obstetrics to overcome uterine inertia in postpartum hemorrhage and during cesarean section. The average dose is 2 to 3 minims given intramuscularly. The other physiologic effects of the posterior lobe have so far no practical application.

The preparations available that contain the two fractions are as follows: Pitocin N. N. R. represents an oxytocic activity of 10 units and pressor activity of $\frac{1}{2}$ unit per cubic centimeter.

Pitressin N. N. R. represents a pressor activity of 20 units and oxytocic activity of less than $\frac{1}{2}$ unit. It also possesses antidiuretic properties.

Pituitrin O (obstetrical) is similar to solution of posterior pituitary U. S. P. and represents 10 oxytocic units per each cubic centimeter.

Anterior Lobe.—The secretions of the anterior lobe are essential for the physical and psychic well being of the individual. Unfortunately none of the anterior lobe hormones have been isolated in sufficiently pure form for clinical conditions in which their use is indicated. The practitioner, therefore, must assume a conservative attitude in regards to the use of injections of the various pituitary hormones. Several of the anterior pituitary hormones (growth, thyrotropic, etc.), however, are available in the laboratory for animal experimentation. There is a great difference between the posterior and anterior lobe extracts. The anterior lobe preparations exert their influence rather slowly, require repeated administration and affect more the structural elements of the body; the posterior lobe preparations provoke immediate pharmacodynamic response. Commercial products representing the growth principle are antuitrin G; pituitary extract and phyone. In addition to the growth hormone they contain a certain amount of gonadotropic and thyrotropic and possibly adrenotropic principles. For clinical use, therefore, they are to be considered as a mixture of the above hormones and not as containing pure growth factor. It would appear that the field of usefulness of growth hormone in pituitary dwarfism will be limited. Pituitary dwarfism is due not alone to the deficiency of the pituitary growth factor but the thyroid, the thymus, the adrenals, the vegetative centers in the diencephalon and

mineral metabolism, etc., are implicated in its etiology.¹¹ One could hardly expect a readjustment of the entire "pathologic personality" to follow the injection of growth hormone. The various sex-stimulating hormones from the anterior pituitary (gynantrin, prephysin, etc.) have so far yielded no convincing results. Anterior pituitary-like substances prepared from the urine of pregnant women (antuitrin S, follutein,



Fig. 186.



Fig. 187.

Fig. 186.—Aged seventeen years. Increase in weight, headaches. No catamenia. Treated with theelin with no results.

Fig. 187.—Same case as Fig. 186. x-Ray of sella turcica revealed erosion of the dorsum sellae and floor of pituitary fossa. Diagnosis: Intraseellar tumor

A.P.L., etc.) will be considered under the heading Female Sex Hormones. It is the clinical experience of many observers that oral administration of desiccated whole pituitary gland is beneficial in some cases of hypopituitarism.¹² However, the extravagant claims made by certain pharmaceutical houses for oral use of pituitary organotherapy must be accepted with some scepticism.

Female Sex Hormones.—The hormones concerned in menstruation are the two ovarian hormones, estrone and progesterone, and the anterior pituitary gonadotropic hormones. In order to use these products intelligently, we must first know what their respective functions are and what we may expect them to accomplish when introduced into the bodies of our patients. Estrone (follicular hormone) stimulates the endometrium to proliferation and promotes development of the secondary sex characters of the female. Progesterone stimulates the endometrium to secretory activity and desensitizes the myometrium to the oxytocic principle of the posterior pituitary, thus, "relaxing" the uterus, preventing painful uterine contractions. Anterior pituitary gonadotropic hormones stimulate the ovary to follicle ripening and luteinization.

Our replacement therapy is, at best, limited to those conditions in which there is a definite deficiency of one of these hormones. The administration of estrone, therefore, is rational only in conditions where there is a proved deficiency of follicular hormone in the blood. (Normal level 1 mouse unit in 40 cc. of blood). This condition exists in most women at the menopause and in about half of the cases of amenorrhea and functional sterility. There is but little to be gained in supplying estrone to amenorrheic women, for only the first half of the cycle, the proliferative phase, is induced and the bleeding which results is not true menstruation. Even if one could supply adequate quantities of estrone and progesterone consecutively and a normal secretory endometrium were induced, the bleeding which would result would occur only as long as treatment were continued. In other words one would have to repeat this form of therapy every month to induce regular menstruation. This is obviously impractical.

A small infantile uterus may oftentimes be stimulated to growth by adequate doses of estrone; 10,000 international units every five days is usually effective in cases of genital hypoplasia due to hypoestrinism. Some men have advised huge doses, 80,000 international units per dose, but this method is inadvisable since it has been known to produce severe headache and other untoward symptoms. Also, theoretically at least, such a dose would tend to inhibit the production of anterior pituitary gonadotropic hormone. This, in turn, would be

followed by ripening of fewer follicles, and such therapy would only defeat our purpose.

In the menopause a great deal of good can be accomplished with adequate doses of estrogenic substance. The vasomotor symptoms appear to be favorably affected by the administration of 10,000 to 50,000 international units of estrone every five days, either intramuscularly or orally. The oral route is probably the better since its effect is continuous and more nearly approaches nature's method of supplying the hormone. However, it has been our experience that cases showing mild menopausal symptoms can be successfully treated by psychotherapy and mild sedatives, particularly phenobarbital and calcium. We had considerable success with a combination containing phenobarbital 0.02 Gm., bellafoline 0.0001 Gm., ergotamine tartrate 0.0003 Gm. in controlling the headache and emotional instability of the menopause. Cases with more severe symptoms should be treated with large enough doses of estrone to inhibit the overacting anterior pituitary gland, since it has been demonstrated that the distressing symptoms, particularly the "hot flash," are due to excessive secretion of gonadotropic hormone. Any improvement which results lasts only as long as the injections are given. Estrone therapy has also proved of some value in juvenile vulvovaginitis and pruritus vulvae of the menopause. In those conditions the hormone is best administered by vaginal suppository. Painful, lumpy breasts (mastopathia) may be successfully treated with large doses of estrogenic substances; similar results may be obtained in the rarer instances of mastopathia in man (Fig. 188).

Progesterone therapy is still in its infancy. Commercial preparations of this hormone have become available for use only recently. Experiments on animals and a few on humans lead us to believe that certain cases of dysmenorrhea and habitual abortion may be successfully treated with this substance. To date, there is not enough clinical evidence of its efficiency and dosage. We have recently used 1 rabbit unit of progesterone every other day for two months in 3 cases of habitual abortion with a successful outcome in 2 of them. Each of these women had aborted spontaneously on two previous occasions.

The preparations, antuitrin S, follutein and A.P.L., most commonly used to replace gonadotropic hormone, do not contain anterior pituitary hormones, but a substance derived from pregnancy urine which has gonadotropic-like properties. This substance does induce follicle ripening and luteinization in immature and hypophysectomized animals. Unfortunately, how-

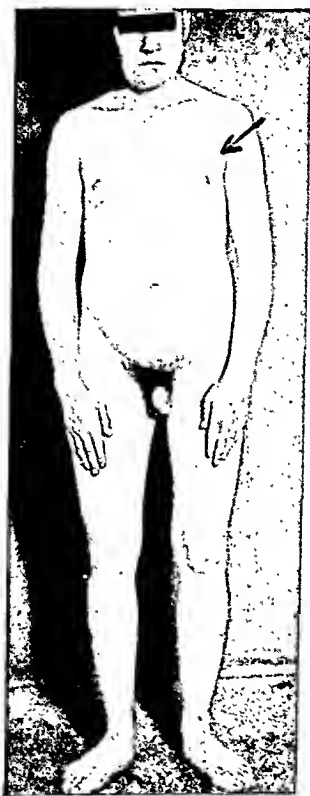


Fig. 188.—Enlarged and painful breasts in male aged twenty-one. Treatment with estrone resulted in complete disappearance of symptoms.

ever, no one has been able to demonstrate similar changes in the human ovaries. Theoretically, gonadotropic therapy would be indicated in cases of amenorrhea, functional sterility, dysmenorrhea, and habitual abortion due to faulty luteinization. Practically, this has not been the case. The only condition in which gonadotropic-like substance has proved of value has been the functional uterine bleeding in young women. The same

type of bleeding in women near the menopause usually does not respond to hormone therapy, and radiation is definitely the treatment of choice. Also, in these older women, the possibility of uterine neoplasm, either benign or malignant, should always be borne in mind. Almost 15 per cent of women who complain of metrorrhagia or menorrhagia at the menopause have been found to suffer from cancer of the genital tract. Therefore, no case of bleeding at the menopause should be treated with endocrine products unless a diagnostic curettage has been performed first.

The *modus operandi* of pregnancy urine extract is rather obscure.

Cryptorchidism.—In boys presenting genital underdevelopment in the form of either hypoplasia or of cryptorchidism, treatment with pregnancy urine extract has proved of definite value.¹³ Two hundred rat units three times weekly for four to eight weeks is the recommended dose. Treatment should be started early at about nine years of age. It is certain that hormonal therapy will often fail; it is also true that some cryptorchic children correct themselves spontaneously at puberty, nevertheless hormone therapy is indicated if the case is seen at an early age. If hormone therapy fails surgery should be resorted to. There is sufficient evidence that pregnancy urine extract exerts profound influence on male genitalia and changes simulating premature puberty may be produced.¹⁴ Boys treated for cryptorchidism with pregnancy urine extract should be carefully observed and treatment stopped before genital growth becomes excessive.

Testosterone—male sex hormone—is produced synthetically and is considered to be identical with the active substance isolated from the testicular tissue. It is available for intramuscular use as testosterone propionate in a solution of sesame oil; the average dose being from 5 to 25 mg. three times weekly. It has been recommended in benign prostatic hypertrophy, organic impotence and hypogonadism.¹⁵ The clinical value in benign prostatic hypertrophy is not well established. However, there is sufficient clinical and experimental evidence to justify the continued use of the hormone in the latter two conditions. Recent animal experimental work by Moore¹⁶ and the clinical application by Mulholland and Soloway¹⁷ points to

the efficacy of testosterone therapy, when applied in a lanolin-like menstruum by inunction.

Adrenal Gland.—The uses of epinephrine, the medullary hormone, are too well known to be discussed here. Derivatives of the cortex, though not clearly defined chemically as yet, can be obtained in the form of extracts which represent mixtures of the active principles. Kendall, who has done much to define the nature of the substances obtainable from the cortex, believes that at least two factors are present, one which is

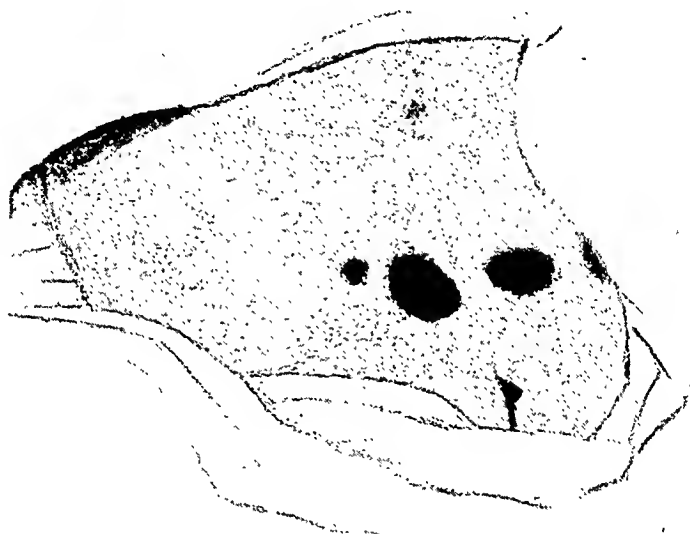


Fig. 189.—Aged fifty-two years. Illustrating pigmentation of a proved case of Addison's disease. The spots on lumbar region and between buttocks were the only pigmented areas present.

related to mineral metabolism, and the other associated with the functions of muscular tissue.¹⁸ That other factors are present in the cortex is indicated by Pottenger and Simonsen,¹⁹ who were able to prepare extracts which had female sex-repressive properties, and male sex-stimulative effects. Many preparations are available; perusal of the literature indicates that 2 of these, eschatin (Parke, Davis & Co.) and adrenal cortex extract (Wilson) have been used extensively and are of established clinical value. Standardization of the adrenal cortex

has proved extremely difficult, and the dog unit can be accepted only as a rough measure of potency. The oral use of adrenal cortex has not been sufficiently tested to make a report here.

Addison's Disease.—During the acute crises of this condition 10 to 50 cc. of adrenal cortex extract must be given intravenously daily. The daily dose is gauged by the clinical condition. It is likewise important to administer intravenously, at the same time, copious amounts (2–4 liters in twenty-four hours) of a solution composed of 10 per cent dextrose, 1 per cent sodium chloride, and 0.5 per cent sodium citrate.

During the chronic stages, adrenal cortex is not so urgently indicated, as it is sometimes possible to maintain patients satisfactorily on a low potassium diet, and, by administration of large oral doses of sodium chloride and sodium citrate. The development of symptoms such as loss of weight and weakness, or the occurrence of illness or infection of any kind, demands the liberal use of adrenal cortex. No definite dosage can be stated, but as a general rule 2 to 5 cc. daily or every other day should be given.

In the absence of pigmentation (Fig. 190) diagnosis is a very difficult problem. Changes in the blood electrolytes are not always apparent during the chronic stages. Blood sodium and chloride values may or may not be lowered, and the blood urea is usually within normal limits. Blood potassium values are occasionally elevated (normal 18–25 mg.) but the technical difficulties involved make such determinations impractical. The potassium tolerance test, as suggested by Zwemer²⁰ cannot be adapted to routine clinical use for this reason. More practical as a diagnostic measure seems the method recently advanced by Cutler *et al.*²¹ Here the patient is placed on a salt-free diet for three days, at the same time receiving 0.033 Gm. of potassium citrate per kilo of body weight. Determination of urinary chlorides is then carried out. Normal figures are around 125 mg. per cent. while in adrenal insufficiency they may exceed 225 mg. per cent. Such determinations may well serve as a guide in the use of adrenal cortex in doubtful cases.

In treating functional types of adrenal insufficiency, doses of 1 to 2 cc. two or three times weekly are adequate to bring about favorable response. In addition, sodium chloride 10 Gm. daily, sodium citrate 5 Gm. daily and a low potassium

diet are included (less than 2 Gm. of total potassium content per day).

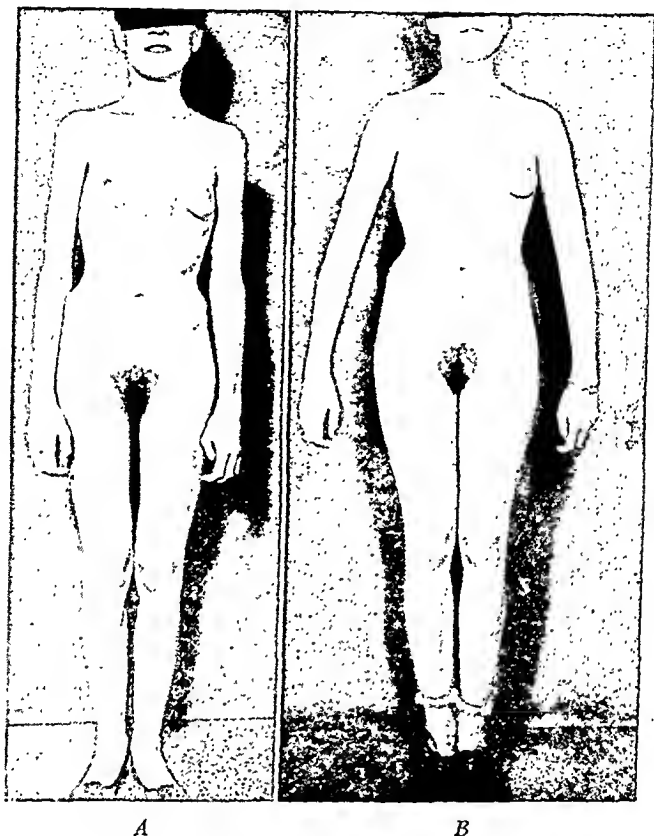


Fig. 190.—*A*, Adrenal insufficiency in a girl sixteen years of age. Loss of weight (25 pounds in twelve months). Extreme fatigue. Cessation of menses. Blood pressure: systolic, 82; diastolic, 70. Basal metabolic rate minus 36 per cent. Blood cholesterol, 145 mg. per cent. Fasting blood sugar, 87 mg. per cent. *x*-Ray of sella turcica, negative. *x*-Ray of chest showed hypoplasia of heart and large vessels. Slight bluish pigmentation of lips and roof of mouth. A course of insulin, thyroid and pituitary extract had no effect. *B*, Same patient after treatment with adrenal cortex, 3 cc. weekly, with high sodium chloride and low potassium diet resulted in gain of 12 pounds in three months and marked improvement in muscle strength.

Simmonds' Disease with Marked Cortical Atrophy.—In view of the marked atrophy of the adrenal cortex in Simmonds' disease, its use here is indicated, particularly where the cortex

may be so atrophic as to be unable to respond to pituitary stimulation. In 1 instance of fatal Simmonds' disease, complete absence of adrenal cortex was noted by Steinfield *et al.*²²

It would seem that a substance so vital to life and maintenance of health would have other clinical applications than those described above. Numerous investigations are in progress to discover its further value. Only a few of these studies can be touched upon here. The close similarity of adrenal insufficiency to shock and clinical states of nonrenal azotemia²³ has led investigators to study the effects of adrenal cortex in many types of shock. Its use here may be beneficial in those instances where the adrenal gland suffers damage.

Wohl *et al.* have indicated that nonrenal azotemia as exemplified by the toxemia of experimental high intestinal obstruction can be successfully combated by simultaneous administration of saline solution and adrenal cortex.²⁴ Animals thus treated lived much longer than untreated controls.

Allergic states have been the object of treatment by adrenal cortex with variable results. Finally, obscure, yet important relations of the adrenal gland to the vitamins, immune processes and infections are being explored, but as yet have no definite application to human disease.

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DIAGNOSIS AND TREATMENT OF GASTRO-
INTESTINAL ALLERGY

ALLERGIC reactions following the ingestion of foods are not unusual but they most often occur in some other mucous membrane surface or the skin rather than the mucosa of the gastro-intestinal tract. In other words, generally some other area is the so-called "shock organ" in which the classical allergic spasm and edema occur. This reaction can come on immediately or may often be delayed for hours. It has still not been determined whether the primary protein is at fault or if the end-product of protein digestion is the allergenic etiologic factor. Many severe edematous paroxysms come on so suddenly that they must be due to the original protein substance.

Occasionally we have gastro-intestinal conditions that so closely follow the ingestion of food to which the patient is sensitive that they must be described as allergic. The allergic manifestation in the gastro-intestinal mucosa can be contact type or can follow systemic absorption of the offending protein. Any mucous membrane surface of the body can be the "shock organ."

At the present time, we believe there is clinical, radiological and laboratory evidence of gastro-intestinal disturbances which are due to food allergy. We can mention some of the most important conditions in which it has been proved by clinical observation that these are due to a hypersensitivity to certain foods. These are acute gastritis and gastro-enteritis; chronic hypertrophic gastritis and enteritis; colitis, particularly mucous colitis; gastric and duodenal ulcer and possibly gastro-

intestinal hemorrhage and hematemesis. Also, less severe manifestations such as stomatitis, mouth ulcers (canker sores), pylorospasm, anorexia, constipation, diarrhea and frequently pruritus ani can be shown to be allergic in origin. We have had 3 cases of severe gastro-intestinal pain due to food allergy. We feel that every other possibility must be eliminated before a diagnosis of allergy is made in any abdominal disorders.

The history in any case of suspected allergic disease is of extreme importance. If an hereditary history of allergy is found or if the patient himself has had previous allergic manifestations, we must be more than ever suspicious of allergy in abdominal conditions of undetermined etiology. It is well to note any allergy in offspring as well as parents. The patient often can remember that the onset or an exacerbation of symptoms followed the taking of certain foods. Seasonal remissions are not uncommon in allergic disorders of the gastro-intestinal tract as in other allergies and other gastro-intestinal diseases.

The x-ray has been used to demonstrate an allergic reaction in the mucosa and musculature of the colon. Films of the colon following the ingestion of a specific food showed in 1 case a hypotonicity of the ascending colon and a hypertonic and spastic transverse colon. After taking the food to which he was hypersensitive, this patient had severe pain which was relieved by injections of epinephrine hydrochloride. Pylorospasm and gastric retention have been shown to be of allergic origin by the roentgenologist. Spasticity of the colon is one of the most usual conditions in which we have had radiological evidence of food hypersensitivity.

It is very difficult to demonstrate edema of the mucosa of the intestinal tract as it is transitory in nature and disappears rapidly at times. One case reported by Gay showed distinct evidence of marked mucosal edema which disappeared on an elimination diet. We have thought at times that it was possible to see thickening on fluoroscopy but certainly cannot go on record that this was due definitely to food allergy. Repeated films should be made before a diagnosis of edema of allergic origin is made.

Laboratory evidence of gastro-intestinal allergy must be evaluated very carefully. Skin tests, both scratch and intra-

cutaneous, are very frequently misleading and many times of no significance. If a markedly positive reaction by either method can be demonstrated by repeating twice, it can possibly be looked upon as significant. To be absolutely sure, passive transfer should always be done. If the Prausnitz-Küstner reaction can be demonstrated, one can be reasonably sure of some degree of food hypersensitivity.

If the skin tests do not give us a clue in a case in which food allergy is suspected, we always have recourse to elimination diets. Excellent lists and books have been provided but a physician is qualified to arrange his own diet of this type for each individual patient.

There is a variance of opinion as to the period of time in which we should expect results. Opinions range from twenty-four hours to one month. One to two weeks would seem to be enough time to find some measure of improvement. Rowe suggests one week to one month depending on the type of case and the length of time the patient has had his symptoms.

Eosinophilia is one hematologic response that is regarded by some as evidence of allergy. This finding is much less constant in so-called "food allergies" than in hay fever, asthma, eczema and other more definite allergic manifestations. It is of course important to rule out parasitic invasion in cases in which the eosinophil count is abnormally high. If an eosinophilia persists and all other conditions have been ruled out, we can regard the condition as suspiciously allergic. In 4 cases, after the offending food protein was eliminated the eosinophil count dropped to normal. One count had been up as high as 23 per cent. An increase in the number of eosinophiles or even a preponderance of this type of cell was not noted in smears taken from the rectal mucosa of a group of patients with a so-called "allergic bowel." This finding is not so persistent and constant as seen in smears from nasal mucous membranes in which the edema is allergic in character. The mucosal smears from 25 cases were examined and in only a few was there a suggestion of an increased eosinophil count. Aside from this group, we have had the privilege of examining the reports on several cases in which there was an increase in eosinophiles but not to any significant degree.

The leukopenic index is believed by some observers to be

of significance in the determination of food allergy specificity. Here again repeated determinations must be done before any conclusions can be reached.

The glucose tolerance determination is of very questionable significance in the patient suspected of gastro-intestinal allergy. A high tolerance for glucose and a low glucose tolerance curve have been found in several of our cases but it is not the rule. Lactose and glucose by mouth have proved efficacious in the treatment of some of these individuals, probably for reasons other than an increased tolerance for carbohydrate.

Hypochlorhydria has been demonstrated in many allergic diseases and it is possible in gastro-intestinal diseases of allergic origin.

Four cases in 10 showed hypo-acidity. This finding was not constant and changed markedly on different determinations.

Sigmoidoscopic examination of the lower bowel in a large percentage of these cases showed practically the same picture we have in nasal allergy. This is usually the pale, pearly, thick, boggy, edematous mucous membrane over the surface of which is a thick gelatinous secretion. At times there is increased arborization of the smaller vessels and occasionally petechial spots rather generalized over the entire lower bowel.

Complete blood chemistry studies were done on a group of individuals suspected of gastro-intestinal allergic manifestations. These determinations included blood chlorides, calcium, phosphorus, plasma CO_2 , serum globulin and albumin, and any other procedure necessary for each individual case. There was no significant change in any of the above readings with the exception of those who had medical conditions, gastro-intestinal or otherwise, which altered the blood chemistry.

At times we have had to make a differential diagnosis in patients with abdominal pain. It is very dangerous to assume that pain in this area is an allergic manifestation. All other possibilities must be eliminated.

Case I.—H. B., a young boy aged thirteen, had seasonal hay fever and perennial asthma of indefinite periodicity for seven years. During a very severe attack of asthma he was suddenly seized with a severe abdominal pain which was generalized at first and later was more pronounced in the right lower quadrant. He had a little nausea but no vomiting. This child had a long

hereditary history of allergy and many previous personal allergic symptoms. One sister and a brother had hay fever. There had never been any previous attacks of abdominal pain. Repeated injections of epinephrine 1:1000 gave no relief except for his asthma. The asthma was no better after the onset of the pain. This is sometimes the case if allergic symptoms change from one location to another. A blood count showed a high percentage of polymorphonuclear cells (84 per cent), 4 per cent eosinophiles and a white count of 18,000. On repeating the count it was approximately the same. Symptoms increased in severity and, on advice of two consultants, an appendectomy was done. The appendix was very acutely inflamed. Ether anesthesia was used and the child was entirely asthma-free during the operation and twenty-four hours following.

Case II.—M. C., female, aged thirty-five, had asthma for one year. There was a possible hereditary history of allergy in the family and one son had severe asthma. This patient had previously two cesarean sections and an appendectomy. She had had severe infantile eczema and migraine. For about one year she had been having severe attacks of abdominal pain which came on gradually at times and at other times very acutely. Her attacks of migraine were much less severe after the onset of abdominal symptoms. Complete relief was obtained by injections of epinephrine 1:1000 dilution, 5 minims. The pain would disappear for about two hours and then gradually and progressively become worse and again be relieved by epinephrine. Repeated blood counts on this patient showed nothing of significance. We were unable at any time to determine the offending allergenic food. Skin tests by both the scratch and intracutaneous methods were negative. Elimination diet of Rowe and several other dietary arrangements gave her relief. At present she is asthma-free and has no gastro-intestinal symptoms.

Case III.—H. E., aged twenty-one, a young man who had frequent attacks of abdominal pain usually following a series of asthmatic attacks. There was a definite hereditary history of allergy and the patient had hay fever and occasional attacks of urticaria. Protein tests were done by both methods and the gastro-intestinal symptoms were better when the patient was put on a diet although the specific food was never definitely detected. His asthmatic symptoms have markedly improved and likewise the abdominal pain has entirely disappeared. Epinephrine injections relieved the abdominal pain as well as the asthma. At present this patient is eating a fairly normal diet without any discomfort.

We have had in the past few years several other cases of abdominal pain which we believe were allergic in origin. A careful differential diagnosis must be made as shown by the case of the boy in acute asthma with acute appendicitis. The epinephrine test is of importance because the allergic manifestations in the abdomen are usually quickly relieved by injections of this preparation.

It is distressing that, in most of our cases, we could not determine specifically the offending protein. In 1 case, it was definitely milk. Any milk foods would produce violent abdominal pain, nausea and diarrhea. Elimination diet is probably the best way of determining the offender.

Pruritus ani is a most annoying symptom and is often seasonal in character, occurring most frequently in the spring and early fall in the cases we have seen. Many cases are also perennial in character.

Case IV.—N. H., female, aged thirty-eight, had pruritus ani and pruritus vulvae for eight months. She was checked and found to have a *Trichomonas vaginalis* infection. This cleared up on treatment but the pruritus persisted. The patient was placed on a diet of milk only for one week and the itching entirely disappeared. Skin tests by the intracutaneous method showed a few moderate reactions to foods. At present the patient is taking 9 foods and has not had any pruritus in the past two months. We are adding 1 or 2 foods weekly to her diet hoping to discover the offending food. Passive transfer tests have not been done on this patient. This shall be done if we can possibly detect any suspicious proteins.

Case V.—A. P., a man aged forty, who has had hay fever and seasonal asthma for eight years. He has had a course of hyposensitization for fall pollens with fair results. In the past two years he has developed pruritus ani during the pollen season only. He was completely tested for foods and showed reactions to quite a few fruits and vegetables. These have been eliminated from his diet but he still has some itching which he feels is worse after the ingestion of certain vegetables. Up to the present, we have not yet determined the etiologic factor but feel that it probably can be found in those foods to which he reacted so markedly by the intracutaneous method of testing. Pollen irritation also may be a factor.

Case VI.—C. W., aged forty-eight, a man who had pruritus ani and severe urgency and frequency of urination following the ingestion of milk or milk products. A small quantity of milk will precipitate an attack in two or three hours and this will persist for two to three days. As long as his diet does not contain milk, he is symptom-free.

We have had the privilege of testing a group of patients with mucous colitis. In some we have found a multiple reactivity and in others very few reactions were noted. Occasionally we find a patient who will give very significant reactions by the scratch test but usually the intracutaneous method is desirable.

Diets arranged according to the skin tests (avoiding reacting proteins) gave us very little help but carefully planned

elimination diets manipulated to suit each individual often proved quite beneficial. A patient can be put on one food for a designated period of time, adding one food at intervals until the offending substance is found. Another plan is to give the patient a small group of foods, change the groups at different periods and in this way determine an immunity to 8 or 10 proteins at one time. The former method is more tedious but more efficacious.

In gastro-intestinal patients who have an hereditary background of allergy and previous or present allergic manifestations, one should always be suspicious of food hypersensitivity. If these patients are not primarily sensitive to a certain food, it is possible to sensitize them to foods of which they are eating large quantities. It has been our experience that more marked skin reactions are elicited by testing for foods which are daily in the diet. The best example is the increasing sensitivity to milk and milk products if an allergic individual is on an ulcer diet.

Some evidence has been shown that allergy is possibly an etiologic factor in peptic ulcer. This has not been investigated to any extent but should be kept in mind in allergic individuals with ulcers.

In all other gastro-intestinal conditions mentioned, at times we have suspected allergy as a causative factor. Conclusive evidence is lacking in most cases but, with a background of allergy in a patient, one should consider a possible protein sensitivity.

Conclusions.—Any area of skin surface or mucous membrane may be the "shock organ" of an allergic reaction. The gastro-intestinal mucosa both by contact and following systemic absorption of a protein can probably be the sensitized area.

Spasm and edema, increased permeability of cell walls and excessive secretion of mucus complete the cycle of most allergic reactions. This syndrome is often present in gastro-intestinal disturbances and may be true allergy.

In patients with a family or personal history of allergy, any symptomatology occurring in any system or organ of the body, within reason, may be allergic in origin. Gastro-intestinal patients who have this background, past or present, should

certainly be investigated from the standpoint of allergy. We believe it is possible to sensitize these patients more easily to extraneous proteins, and diets should be as varied as possible to eliminate this factor.

All other organic and functional disturbances should be eliminated before a diagnosis of gastro-intestinal allergy is made. Skin tests, both scratch and intracutaneous, should be done though they are often misleading but diets should take into account these sensitivity tests. The hypodermic injection of epinephrine often is an adjunct in diagnosis and treatment. x-Ray and laboratory studies are of some assistance in establishing a diagnosis of an allergic reaction.

Carefully planned elimination diets for each individual prove highly beneficial at times. The type of diet and the interval of time between changes should vary with the symptomatology and the condition of the patient. Results are very often disappointing but at times miraculous.

The usual routine of therapy applied to other allergic disorders can be used in cases suspected of gastro-intestinal allergy. Elimination and hyposensitization, specific and non-specific, should be tried first, then drugs and endocrine preparations used in other allergic diseases should be added when indicated.

We are greatly indebted to the gastro-intestinal department of the Graduate Hospital of the University of Pennsylvania for studying and referring many of these cases to us.

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